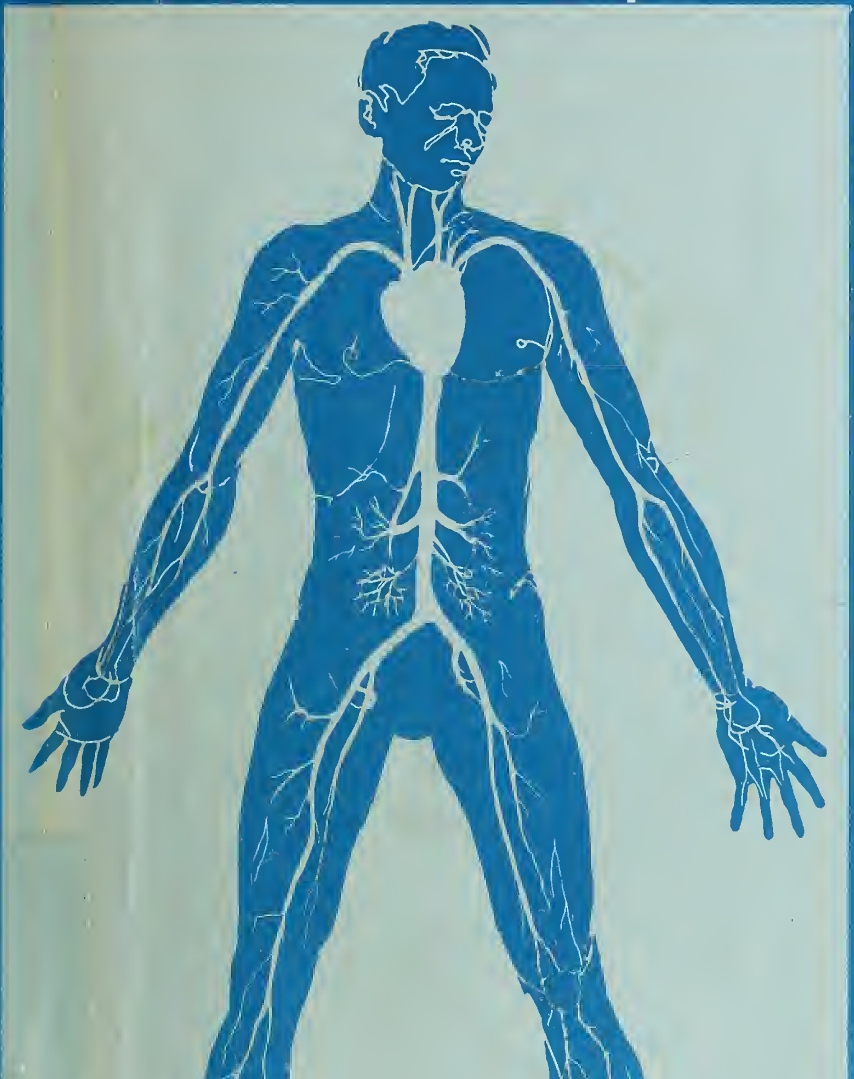
ARTERIOSCLEROSIS

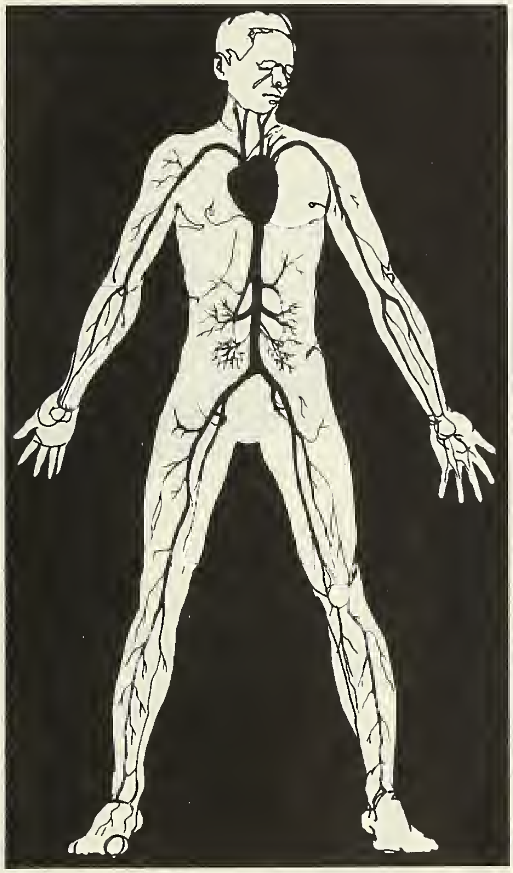
REPORT BY NATIONAL HEART AND LUNG INSTITUTE TASK FORCE ON ARTERIOSCLEROSIS



Vol. II

June 1971

ARTERIOSCLEROSIS



A
REPORT
BY THE
NATIONAL
HEART
AND LUNG
INSTITUTE
TASK FORCE
ON
ARTERIOSCLEROSIS

NATIONAL
INSTITUTES
OF HEALTH

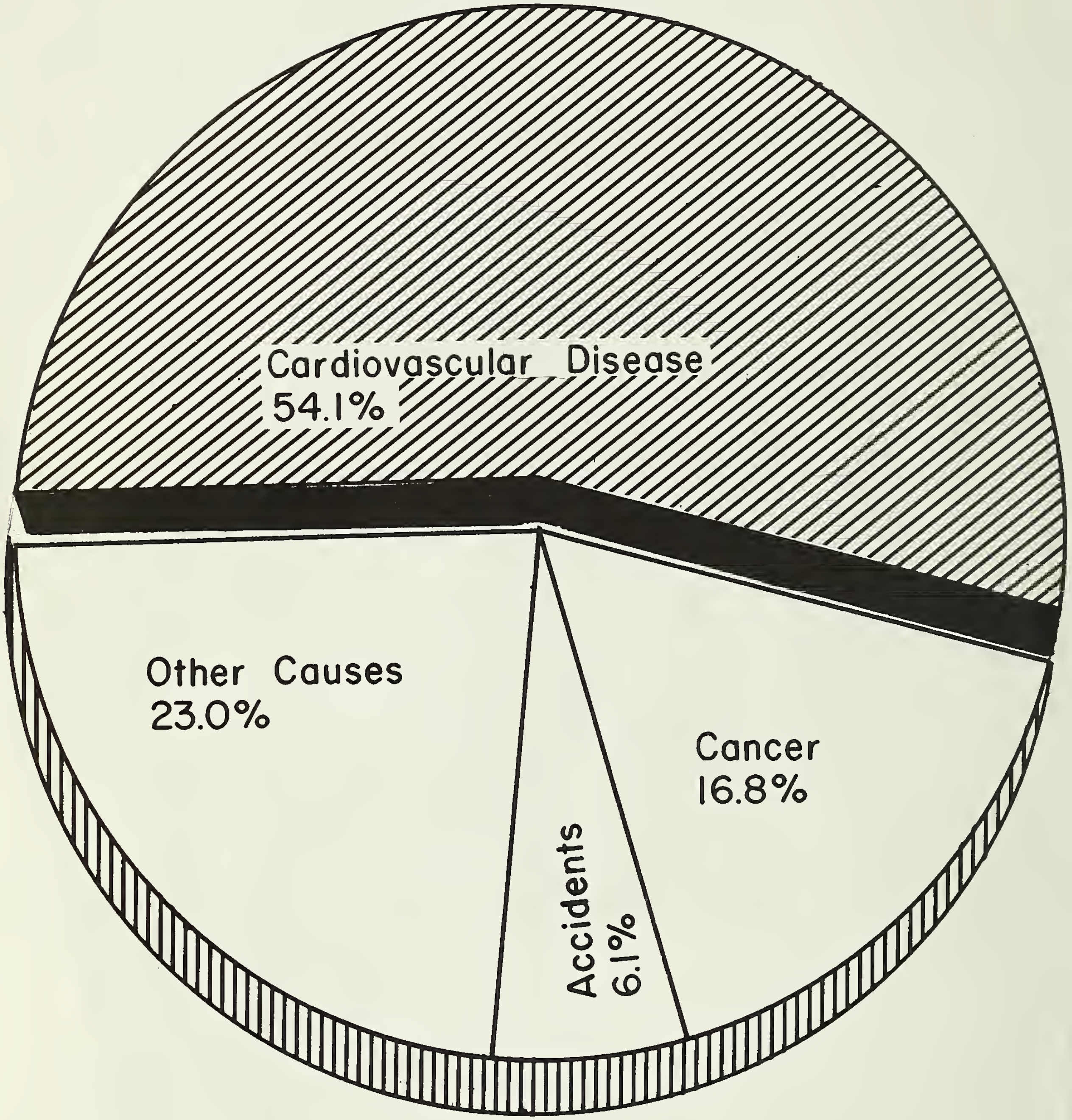
Vol. II June 1971

DHEW Publication No. (NIH) 72-219

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 - Price $2.75

RC
692
.T198
[illegible]
V.2

DEATHS FROM ALL CAUSES, U.S., 1967



"To him who devotes his life to science, nothing can give more happiness than increasing the number of discoveries, but his cup of joy is full when the results of his studies immediately find practical applications."

"There are not two sciences. There is only science and the application of science and these two activities are linked as the fruit is to the tree."

Louis Pasteur (1822-1895)

NATIONAL HEART AND LUNG INSTITUTE

TASK FORCE ON ARTERIOSCLEROSIS

Chairman

Elliot V. Newman, M.D.
Professor of Experimental Medicine
Vanderbilt University
School of Medicine
Nashville, Tennessee

Vice-Chairman

Oglesby Paul, M.D.
Professor of Medicine
Northwestern University
Medical School
Chicago, Illinois

****

Sidney Blumenthal, M.D.
Professor of Pediatric Cardiology
and Associate Dean
University of Miami College of Medicine
Miami, Florida

Kenneth M. Brinkhous, M.D.
Alumni Distinguished Professor and Chairman
Department of Pathology
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

Howard A. Eder, M.D.
Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Alfred P. Fishman, M.D.
Professor of Medicine and Associate Dean
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Charles K. Friedberg, M.D.
Clinical Professor of Medicine
Mount Sinai School of Medicine
Consulting Cardiologist
Mount Sinai Hospital
New York, New York

Herbert P. Galliher, Ph.D.
Professor of Industrial Engineering
University of Michigan
Ann Arbor, Michigan

Jack C. Geer, M.D.
Professor and Chairman
of Pathology
Ohio State University
School of Medicine
Columbus, Ohio

T. Joseph Reeves, M.D.
Professor and Chairman
Department of Medicine
University of Alabama
Birmingham, Alabama

Isadore Rosenfeld, M.D.
Clinical Associate Professor
of Medicine
Cornell University Medical
College
New York, New York

Fiorindo A. Simeone, M.D.
Professor of Medical Sciences
Brown University
Surgeon in Chief
Miriam Hospital
Providence, Rhode Island

James F. Toole, M.D.
Teagle Professor of Neurology
and Chairman of Department
Bowman-Gray School of Medicine
at Wake Forest
Winston-Salem, North Carolina

Ernest L. Wynder, M.D.
President
American Health Foundation
New York, New York

Donald B. Zilversmit, Ph.D.
Professor
Graduate School of Nutrition
Cornell University
Ithaca, New York

Special Consultant

Thomas J. Thom
Statistician
Biometrics Research Branch
National Heart and Lung
Institute
Bethesda, Maryland

NATIONAL HEART AND LUNG INSTITUTE STAFF

William Ellis, M.D.
Office of Program Planning
and Evaluation

Harold H. Fogelman, M.D.
Office of Program Planning
and Evaluation

Ruth Johnsson Hegyeli, M.D.
Office of Program Planning
and Evaluation

Robert L. Ringler, Ph.D.
Deputy Director

VOLUME II

TABLE OF CONTENTS

I. INTRODUCTION.. 1

II. ATHEROGENESIS.. 4

A. The Lesion.. 4
B. Thrombosis.. 27

III. RISK FACTORS.. 43

A. Lipids and Lipoproteins.. 47

1. Relationship between arteriosclerosis and lipids and lipoproteins.. 47
2. Therapeutic modalities for lowering serum lipids and lipoproteins.. 57

B. Hypertension.. 71
C. Smoking.. 80
D. Diabetes Mellitus.. 100
E. Obesity.. 104
F. Physical Inactivity.. 108
G. Genetic Aspects.. 124
H. Psychosocial Factors.. 132
I. Multiple Risk Factors.. 144
J. Statement to the Public on Risk Factors.. 148

IV. PRESYMPTOMATIC ATHEROSCLEROTIC DISEASE.. 150

A. Coronary.. 150
B. Cerebral.. 164
C. Peripheral.. 179
D. Pulmonary.. 187

V. OVERT ATHEROSCLEROTIC DISEASE.. 189

A. Coronary.. 189
B. Cerebral.. 212
C. Peripheral.. 224
D. Pulmonary.. 239

VI. REHABILITATION.. 241

VII. INVESTIGATOR INITIATED RESEARCH.. 245

VIII. APPENDIX

A. Acknowledgements.. 249

B. Names of Panel Members.................................. 250
C. The Magnitude of the Problem............................ 267
D. Economic Impact of Arteriosclerosis..................... 311
E. Impact of Basic Research................................ 356

I. INTRODUCTION

Arteriosclerosis is the chief cause of death in the United States. Its victims, predominantly men, are frequently heads of households unexpectedly taken from their families at the prime of their productive lives. The cumulative personal and social losses are appalling.

Disappointingly, the United States ranks 24th in the world with respect to life expectancy for men. The high mortality from arteriosclerosis is one of the major contributing factors to this shortened life expectancy. The extent of the problem is exemplified by mortality from coronary heart disease, one of the major clinical manifestations of arteriosclerosis. In Denmark, Norway, and Sweden the mortality rate for men under the age of 55 is less than half that for the same age group in the United States. For Japanese men between the ages of 35 and 64, the death rate is 64 deaths per 100,000 population, compared to 400 deaths per 100,000 in the United States; a six-fold difference. Although attempts to learn why the United States fares so poorly in these comparisons have not been conclusive, studies have suggested that differences in diet, life-style, and personal habits may be important. Even more significantly, these studies have emphasized that arteriosclerosis is preventable and that certain influences called "risk factors" may be of particular etiologic importance.

Much thought and investigation already has been devoted to such risk factors as elevated blood lipid levels, hypertension, cigarette smoking and obesity. However, much more remains to be learned about the role of these and other factors and their interplay in the genesis of arteriosclerosis. Many authorities feel that proper application now of existing knowledge would decrease illness and death from arteriosclerosis.

Accordingly, Dr. Theodore Cooper, Director of the National Heart and Lung Institute, convened a Task Force on July 9, 1970, to develop a long-range plan to combat arteriosclerosis. The goal was a program aimed at prevention and control of the disorder, and effective treatment of its complications.

This report contains the results of one year of deliberations by the Task Force. The members met at regular monthly intervals to assess the magnitude of the problem of arteriosclerosis, to develop an understanding of its economic and social consequences, to evaluate currently available scientific information on the disease, to evolve conclusions and recommendations, and to formulate a long-range program for their implementation. The enormity of the problem necessitated the convening of panels of experts (see Appendix B) to assist the Task Force in carrying out its charge.

Three general conclusions could readily be reached at the end of these deliberations. First, an extraordinary amount of useful and highly relevant information bearing on this complex disease has been obtained from the research already completed in this country and others during the past 20 years. Second, this research has led to new knowledge which should be more fully exploited by the National Heart and Lung Institute to the advantage of the citizens of this country and third, despite these important new data the totality of existing knowledge, especially as it relates to the basic causes of the disease, does not permit efficient or comprehensive control of either atherosclerosis or its complications, such as heart disease, stroke, kidney failure or peripheral vascular disease. Thus, the logical recommendations that follow from these conclusions are that this country should: 1) without *delay, develop effective mechanisms for the exploitation of existing knowledge; and 2) recognize the necessity for continued and accelerated research at the most basic level, seeking information which will afford ultimate control of this important disease.*

The report is published in two volumes of which this is the second. Volume I deals with general aspects of the problem and presents the major conclusions and recommendations. In order to communicate this information to interested and concerned individuals, who may be unfamiliar with medical terminology, an attempt has been made to present Volume I in non-technical language. Volume II contains technical information on the current state of knowledge and conclusions and recommendations in each of the following areas: Atherogenesis, Risk Factors, Presymptomatic Atherosclerotic Disease, Overt Atherosclerotic Disease, and Rehabilitation. In a few instances the same material has been included in Volumes I and II to facilitate understanding of several major recommendations.

This report would not have been possible without the assistance of the individuals listed in appendix A, and the expert witnesses who made up the panels listed in appendix B.

II. ATHEROGENESIS

A. THE LESION

Current State of Knowledge

The lesions of atherosclerosis are found in large and medium-sized arteries and affect primarily the intima. The lesions are characterized by progressive accumulations of lipids and increasing fibrous thickening of localized areas of the intima. Atherosclerotic lesions may be classified into three types on the basis of their appearance to the unaided eye: 1) fatty streaks, 2) fibrous plaques, and 3) complicated lesions. Microscopically each of these lesions varies widely in cellular and connective tissue composition. In addition to compromising the blood supply by narrowing the lumen of the vessel, the lesions may cause clinical disease by predisposing to thrombosis or by weakening the affected artery resulting in an aneurysm. Certain segments of the arterial tree are more prone to develop atherosclerotic lesions than others. The principal locations of the lesions are the aorta and its major branches, the coronary arteries, and the larger arteries of the brain. Characteristically, the lesions appear earlier in some arteries than in others. In general, the time sequence of appearance is the aorta, the coronary arteries, and the cerebral arteries. The histology of a normal coronary artery is shown in Figure 1.

The first gross evidence of atherosclerosis is the fatty streak (Figure 2). It consists of an intimal accumulation of lipid associated with an increase in intimal cells. This lesion is typically sessile, and does not cause any significant degree of obstruction of the vessel. Therefore, it does not cause clinical disease. The lesions associated with clinical disease are

FIGURE 1

A section of coronary artery from a three-year old child with no evidence of atherosclerosis (H&E; X190) (AFIP Neg. 56-23037).

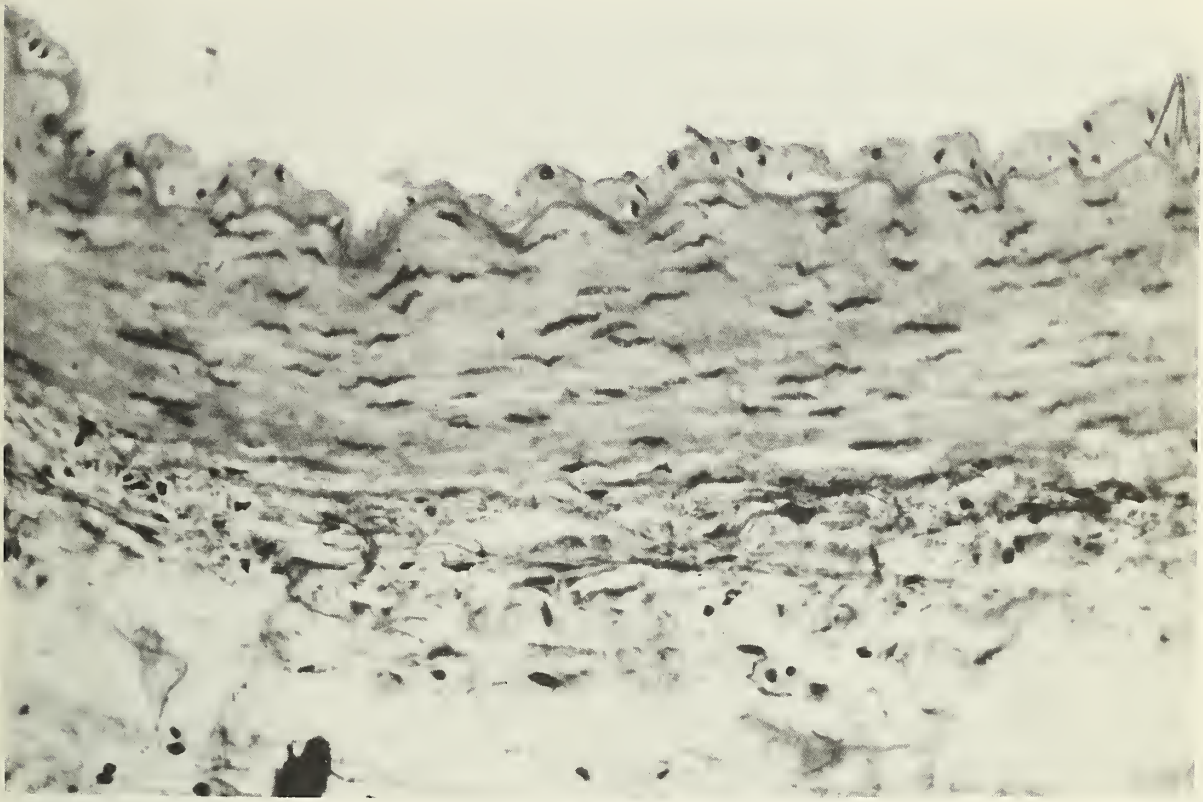
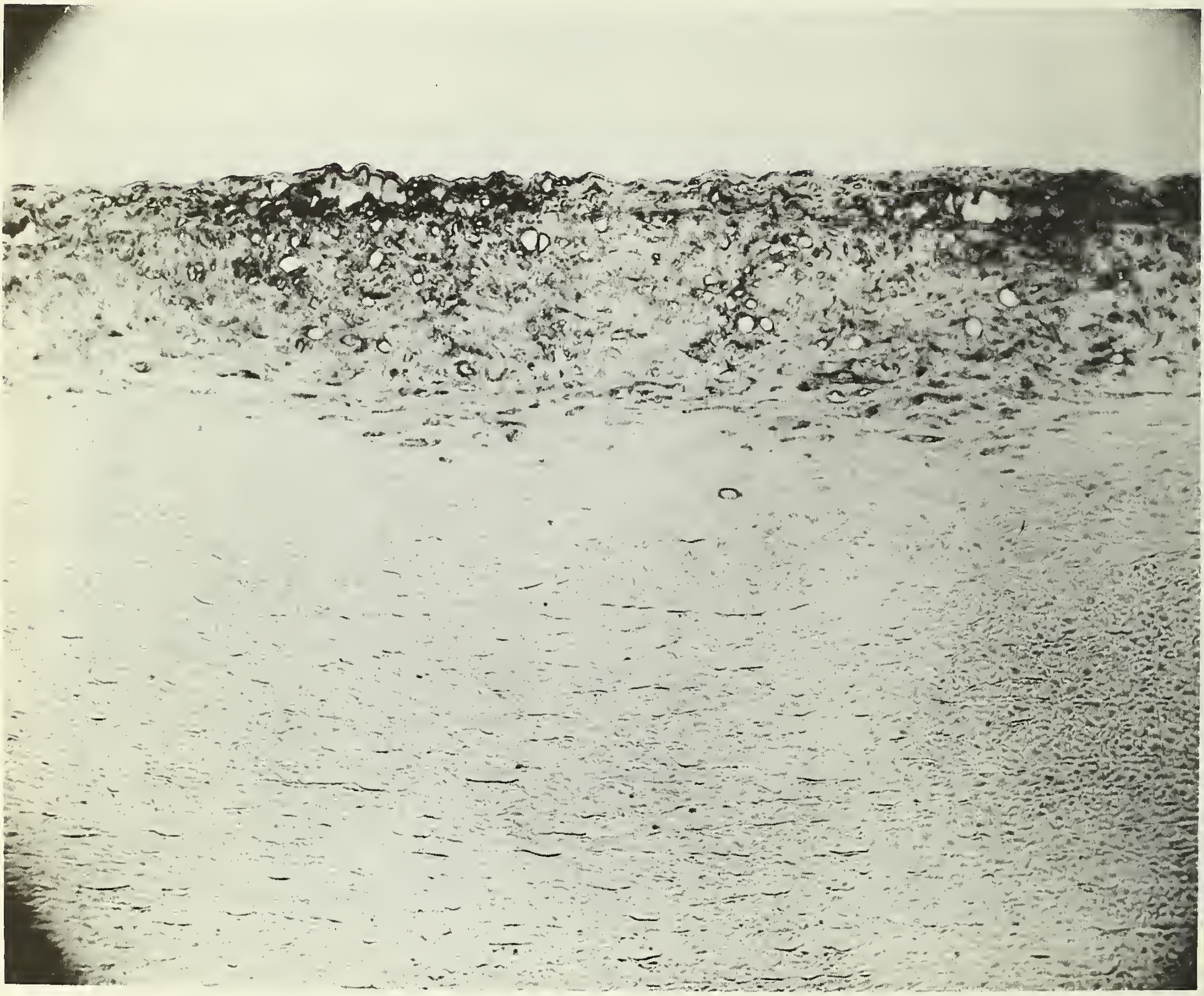


FIGURE 2

Micrograph of fatty streak lesion from the abdominal segment of of the aorta (Oil-red-O and hematoxylin).



fibrous plaques and complicated lesions. The fibrous plaque is raised and protrudes into the vessel lumen. Histologically, it consists of a central core of lipid lying free in the vessel wall and covered on the lumen side by a fibromuscular layer of tissue which may be several times the thickness of the normal intima (Figures 3 and 4). The complicated lesion is a fibrous plaque with various degrees of degenerative change such as hemorrhage into the lesion, mural thrombosis, ulceration, or calcification.

The age at which fatty streaks first appear varies in the different segments of the arterial vasculature. The earliest lesions occur in the aorta and can be observed in infancy. By the age of 10 years fatty streaks are present in the aorta of every child regardless of race, sex, or environment. The extent of aortic intimal surface covered by fatty streaks increases with age from about 10 percent at age 10 years to 30-50 percent by age 25 years. Populations that vary widely in incidence and prevalence of disease due to atherosclerosis later in life show only slight or insignificant differences in the extent of aortic fatty streaks early in life. Coronary artery fatty streaks are first observed at about 15 years of age and increase in surface extent with age. The extent of coronary artery fatty streaks early in life is a better predictor for clinically significant lesions later in life than are fatty streaks in the aorta. Up to age 34, the incidence and extent of fatty streaks in the cerebral arteries (carotid, vertebral, and intracranial arteries) are similar in populations that vary widely in incidence and prevalence of cerebrovascular disease; beyond 34 years of age the extent of fatty streaks and plaques is greater in populations with a high incidence of cerebrovascular disease. The age at which fatty streaks appear in the

FIGURE 3

A longitudinal section of coronary artery with an atheroma. Deep in the intima there is an accumulation of fatty material which is predominantly in macrophages. Between this lesion and the lumen, there is a fibrous plaque. (H&E; X22) (AFIP NEG. 56-6343).

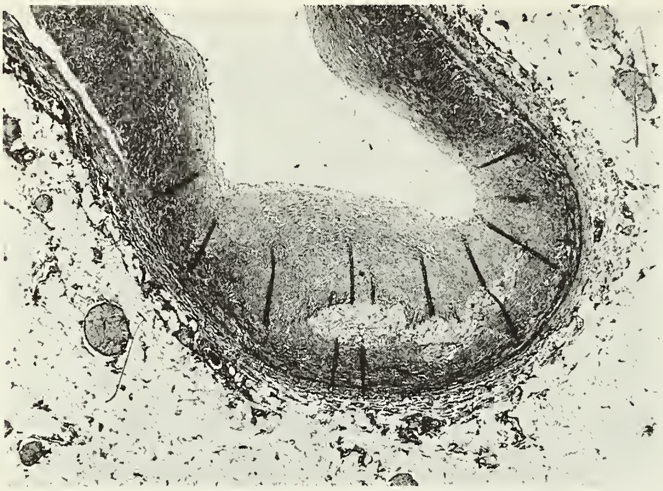
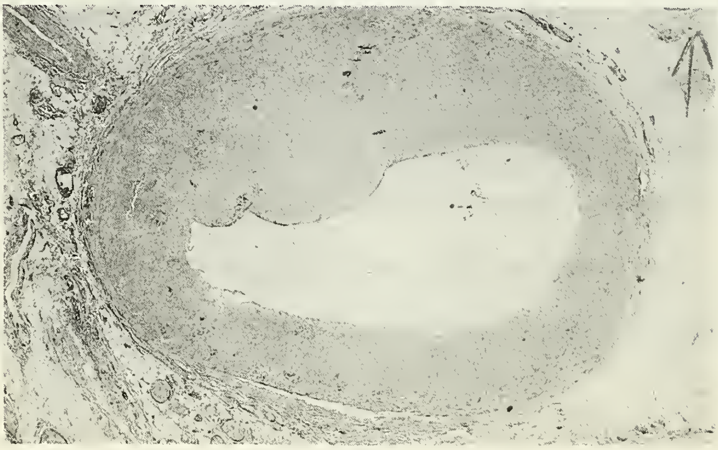


FIGURE 4

A section of coronary artery with more advanced atherosclerosis with a thick fibrous plaque. The amount of lipid in this atheroma is relatively small. The focal involvement with minimal pathologic changes in the opposite wall is the usual morphologic pattern. (H&E; X14) (AFIP NEG. 56-6662).



various cerebral arteries differs; lesions in the vertebral and intracranial arteries appear one to two decades later than those in the carotid arteries.[1,2]

Considering fibrous plaques and complicated lesions collectively as raised lesions there is wide variation in the prevalence and extent of these lesions among populations with different degrees of clinical disease. The populations with the highest incidence of raised lesions in their arteries also have the highest incidence and prevalence of clinical disease due to atherosclerosis. The extent of intimal coverage by raised lesions may vary as much as threefold between populations with high and low incidence of disease. These lesions generally are first apparent in the aorta, coronary, and carotid arteries between ages 25 and 30 years. In the vertebral and intracranial cerebral arteries raised lesions are not generally seen until one to two decades later.[2]

The reasons for the differing susceptibility of various segments of the arterial tree to atherosclerosis have not been explained. Further, in any given arterial segment the distribution of the lesions is characteristically spotty.

Why the lesions in the intima are localized and not diffuse has not been satisfactorily explained. Hemodynamic forces and arterial wall stresses incident to anatomical vessel fixation have been offered as a possible explanation of sites of susceptibility and lesion localization, but such forces alone cannot totally explain the phenomenon. Hemodynamic forces and anatomic fixation of arteries are common to all men while the extent of arterial plaques varies widely. Other etiological factors must be present; perhaps such factors act in concert or discord with hemodynamic forces and anatomic fixation in arteries.

Relation of Fatty Streaks to Plaques. The relation of fatty streaks to fibrous plaques is a question that is desperately in need of clarification. The fact that fatty streaks are present in all populations regardless of their propensity to develop plaques and clinical disease is difficult to reconcile with the thesis that they are an early stage of plaque formation. Further, the fact that fibrous plaques develop in a different segment of the aorta from that in which fatty streaks are seen earlier in life has been offered as evidence that fatty streaks and fibrous plaques are unrelated.[3] Counter to the last argument is the finding that in coronary arteries and extracranial cerebral arteries fibrous plaques are found at the same anatomic location where fatty streaks are observed earlier in life.[2] The panel of pathologists (Appendix B) appearing before the Task Force felt strongly that fatty streaks are an early stage of fibrous plaque formation. They expressed the opinion that fatty streaks vary in their potential, i.e., some regress, some are static, and some progress to plaques. A difference in structure or chemical composition between fatty streaks in various anatomical locations has not yet been found to correlate with their fate.

Initial Lesion. Many investigators through the years have proposed that there is some local injury and reaction in an artery that precedes and predisposes to lipid deposition. Such a local injury and reaction has often been referred to as the "initial lesion."[4] The basic question is whether lipid deposition is secondary to some alteration in the arterial intima, or

FIGURE 5

A section of coronary artery illustrating an atheroma with hemorrhage (upper left) associated with loss of intimal continuity and superimposed recent thrombosis which occludes the lumen. (H&E; X14) (AFIP Neg. 54-967-4).

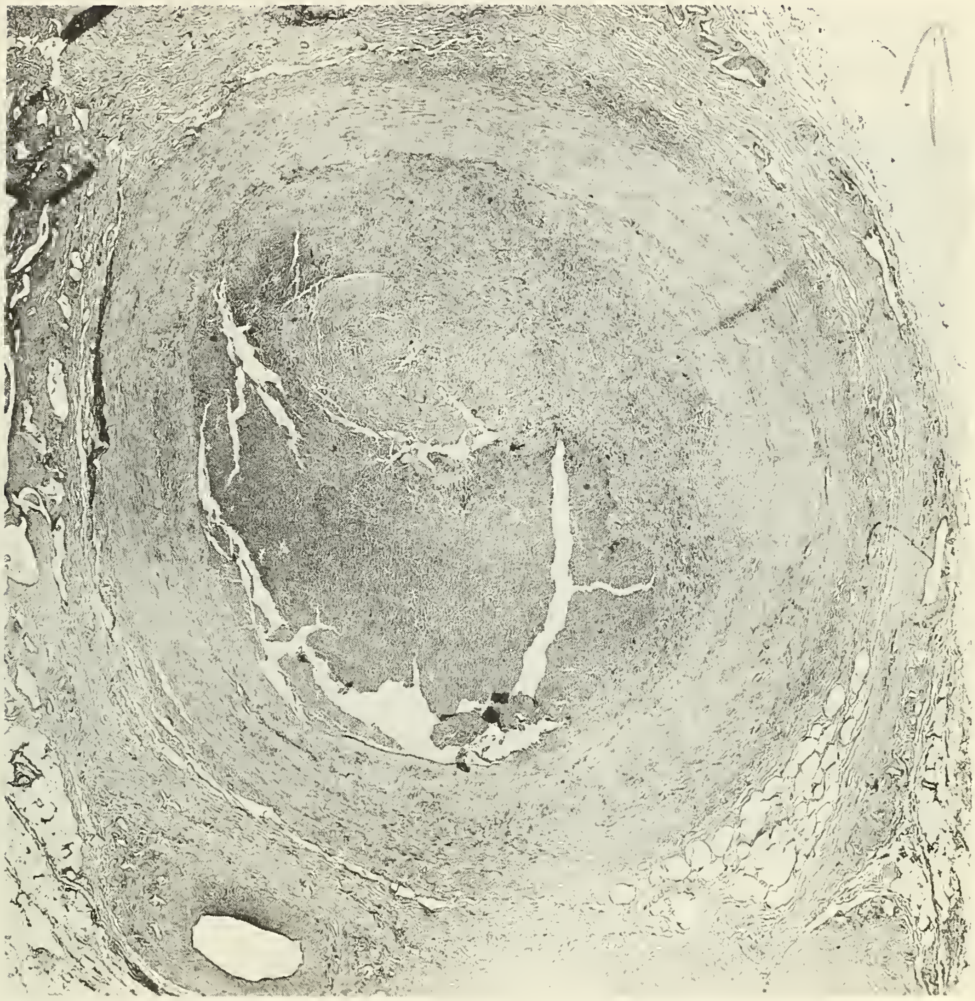
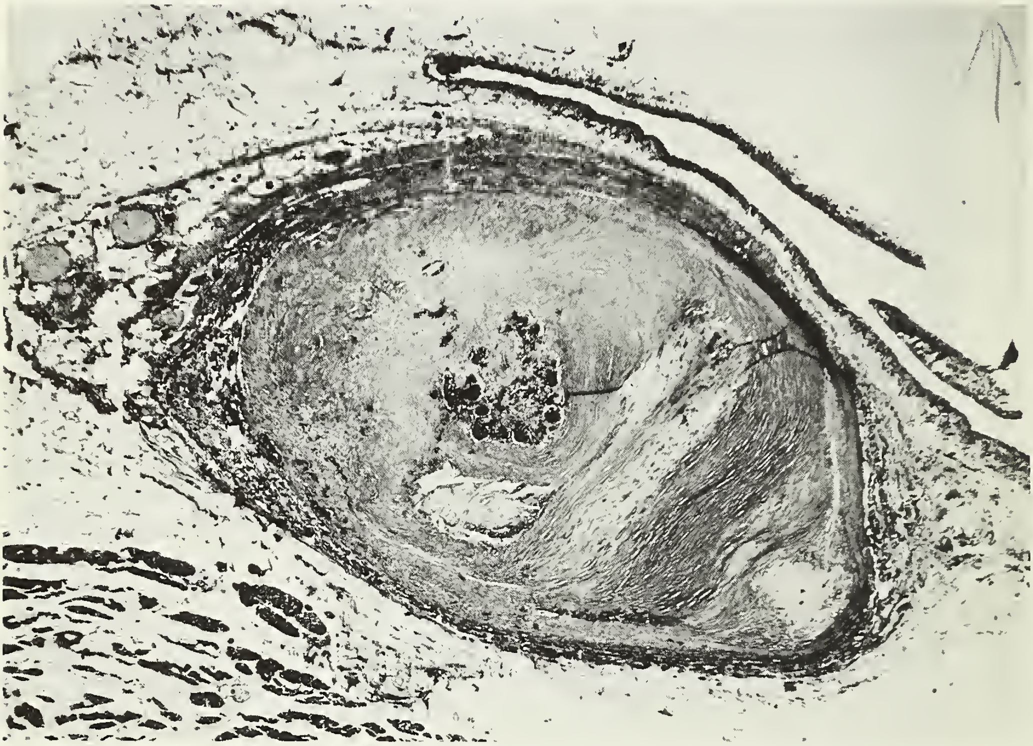


FIGURE 6

A section of coronary artery with advanced atherosclerosis and a central organized thrombus that is recanalized. Beneath the organized thrombus is a small collection of extracellular lipid with focal calcification. (H&E; X12) (AFIP Neg. 60-2426).



whether it is the cause of the alteration. Local changes in amount, type or physical properties of mucopolysaccharides may represent the initial lesion. A local defect in enzyme activity has also been proposed as an initial lesion predisposing to lipid deposition. The problem in accepting any of these proposals, or indeed the very concept of an initial lesion, is our inability to observe and study a single site in the arterial vasculature more than once. Thus, any proposal of what might have happened to a given area of arterial intima at an earlier or a later date is speculation.[4]

A possible initial lesion of atherosclerosis is the fibromusculoelastic intimal thickening that is observed in certain segments of human arteries. It has been observed that those segments of the arterial vasculature that are most likely to develop atherosclerotic lesions are the same as those where intimal thickening occurs.[5] The most striking example of this is the coronary artery where intimal thickening begins at or before birth and continues until about age 30 years.[2] Other sites of intimal thickening are the abdominal segment of the aorta, the iliac and femoral arteries, and sites of branching from large arteries, each of which represents sites where plaques are commonly found later in life. Fibromusculoelastic intimal thickening has been studied most intensively in the coronary arteries, where it is greatest in the proximal portions and diminishes in magnitude distally. The prevalence and magnitude of intimal thickening of the coronary artery have been found to be similar in diverse population groups although these same populations vary widely in incidence and prevalence of coronary heart disease.[2]

Thus it is evident that in the coronary vasculature the presence and magnitude of intimal thickening does not of itself determine whether atherosclerotic plaques will develop. The thickened intima may be more susceptible to lipid deposition, and thus to atherosclerosis, than normal intima when forces operate that promote lipid deposition.

Experimental work has indicated that incident to hyperlipidemia, lipid deposition in spontaneous arterial plaques is greater than in adjacent areas of normal intima of the same artery.[6-10] If intimal thickening does predispose to development of atherosclerotic lesions in the human we must conclude, on the basis of the ubiquity of intimal thickening, that all humans are predisposed to atherosclerosis.

The fatty streak lesion has been the target of most of the morphological and chemical studies done both in man and with experimental models. Experimental studies have repeatedly shown that the induction of hyperlipidemia will induce fatty streaks, usually in the aorta, if the level of serum lipids and time of exposure are sufficient. The chemical composition of human fatty streaks is similar to that of experimental fatty streaks being composed largely of cholesterol, mostly cholesteryl esters.[11] Studies with isotopically labelled cholesterol have demonstrated that nearly all of the cholesterol in the lesions is derived from the blood plasma.[12] Other studies suggest that a protein component of plasma β-lipoprotein is present in the lesions.[12] These observations have led to the tentative conclusion that plasma β-lipoprotein is transported from the blood through the endothelium into the intima. The mechanism by which this transport occurs is unknown.

Morphological and biochemical studies have provided some information regarding the fate of lipid once in the arterial intima. Numerous investigators have shown accumulation of lipid-containing vacuoles in smooth muscle cells and have proposed that the foam cells observed in the lesions are derived from smooth muscle cells.[13] Nevertheless, there is controversy as to whether all the cells in the lesion are of smooth muscle origin.[4] Some investigators have offered evidence that mononuclear type cells probably derived from the blood are present in the lesion and give rise to the foam cells.[4]

Whether or not the smooth muscle cell is the key cell in the atherosclerotic lesion is an important question with regard to the ultimate fate of the lesion--steady state, regression, or progression. Clearly the smooth muscle cell plays an important role in the evolution of the lesion. In addition to accumulating cytoplasmic lipid, smooth muscle cells have been shown to have the capacity for elaborating precursors of the structural elements of connective tissue: elastin, collagen, microfibrils, and basement membrane. Several laboratories currently are growing smooth muscle cells of arterial origin *in vitro* and studying their capacity for lipid accumulation and connective tissue synthesis. Such studies should add immeasurably to our knowledge of lipid transport into and out of these cells and the stimuli to connective tissue elaboration.

Metabolism of the arterial wall has been studied primarily in the normal artery and the fatty streak lesions.[11] Oxygen consumption in the normal arterial wall is very low relative to that of liver or kidney and does not change with aging, whereas oxygen consumption in an artery with fatty streaks is increased over that of a normal artery. With aging or in the presence of fatty streaks, adenosine triphosphate (ATP) production is less than that predicted from oxygen consumption, suggesting uncoupling of oxidative phosphorylation. Approximately 50 percent of ATP produced is from glucose consumption, and the substrate for the remaining ATP production is probably free fatty acid.

Glucose utilization in arteries is primarily by glycolysis to lactic acid. The rate of synthesis of phospholipids, fatty acids, and sterols in arteries with fatty streaks is greater than that in normal arteries. The fatty acid composition of cholesteryl esters in fatty streaks differs significantly from that of cholesteryl esters in plasma, reflecting perhaps esterification of plasma-derived free cholesterol in the artery wall. Present knowledge of arterial wall metabolism is fragmentary and is insufficient to describe the pathogenesis of the atherosclerotic lesion.[4]

The belief is generally held that fatty streaks are reversible lesions. This belief is based more upon faith and speculation than scientific information. Fifty years ago it was noted that in infancy aortic fatty streaks were found mainly over the aortic valve ring and in the first portion of the arch of the aorta; aortic fatty streaks in adolescents are found in the descending thoracic segment of the aorta; and fatty streaks and plaques later in life are found in the abdominal segment of the aorta. This sequence of observations was interpreted to demonstrate that fatty streaks in the more proximal segments of the aorta regress. The experimental studies of Anitschkow are classic in this regard.[14] He observed that the lesions of cholesterol-fed rabbits after cessation of cholesterol feeding undergo a metamorphosis from an intimal hillock of foam cells to lesions smaller in volume composed of a core of extracellular lipid with an overlying fibromuscular cap.[14] This volume change suggests regression. However, the morphology of the lesion after cessation of cholesterol feeding is more like that of a plaque than a fatty streak. The fatty streak regression experiment has been repeated recently in a subhuman primate.[15] It is difficult to determine whether the experimental studies show regression of the fatty streak or progression to a plaque. If the observed "regression" lesions become vascularized as has been demonstrated in one study,[16] these lesions may with time increase in mass by the mechanisms that cause fibrous plaques to increase. A long-term follow-up of such lesions has not yet been done.

Fibrous Plaque Lesions. With presently available information we can only speculate on the factors that cause fibrous plaques to increase in mass. These factors may be the same as those leading to the initial lesion. Three possible mechanisms have been proposed: lipid accumulation, hemorrhage, and mural thrombosis. These mechanisms are not mutually exclusive and could well operate simultaneously. It is also quite possible that there are other yet to be discovered mechanisms by which plaques grow.

The first mechanism by which plaques might increase in mass is by continuous lipid accumulation from the blood. This mechanism could be the same one that generates fatty streaks. The stimulus for the change of a fatty streak lesion to a fibrous plaque has been thought by some to be necrosis of lipid-containing cells with release of lipid into the extracellular space. The extracellular lipid stimulates fibrous connective tissue formation with the extracellular mass of lipid forming the core of the fibrous plaque. By some yet to be discovered mechanism fibrous plaques can become vascularized. These blood vessels arise from adventitial vessels and may also arise from the lumen of the artery.

Hemorrhage from vessels at the base of a fibrous plaque is commonly observed and represents a second mechanism by which plaques can increase in mass. The cause of these hemorrhages is unknown. Certain proposed risk factors (hypertension, anoxia (smoking?), mechanical stress) may exert their effect in part or totally by causing such hemorrhages. Hemorrhage into plaques also has been demonstrated on the basis of cracks or fissures developing in the fibrous cap with extravasation of blood into the plaque from the lumen of the artery.[16] The cause of the fissures has been proposed to be mechanical, i.e. the result of pulsatile pressure acting on a rigid segment of the arterial wall. Another possible cause is hemorrhage into the lesion from small vessels at the base of the atheroma, leading to expansion and bursting of the lesion.

Mural thrombosis is the third mechanism by which plaques increase in mass. Thrombosis is without question a common mechanism, yet the stimulus for the formation of the mural thrombus is not known. Cracks or fissures could lead to formation of a thrombus by virtue of interruption of the smooth endothelial surface. Changes in hemodynamics due to protrusion of the plaque into the lumen of the vessel may be an additional factor in thrombus formation (Figures 4-7).

The mechanisms by which plaques increase in mass very likely are the same as those that initiate clinical disease. The sudden development of symptoms due to rapidly developing arterial obstruction is usually caused by thrombosis. Plaque hemorrhage and rupture also can give rise to atheromatous embolism causing transient or permanent tissue changes in the distribution of the artery, e.g., myocardial infarction and fibrosis, transient cerebral ischemic attacks, or microinfarcts in the brain. The exact sequence of events that

FIGURE 7

A higher power view of the organized thrombus in Figure 5.

(H&E; X80) (AFIP Neg. 61-5026).

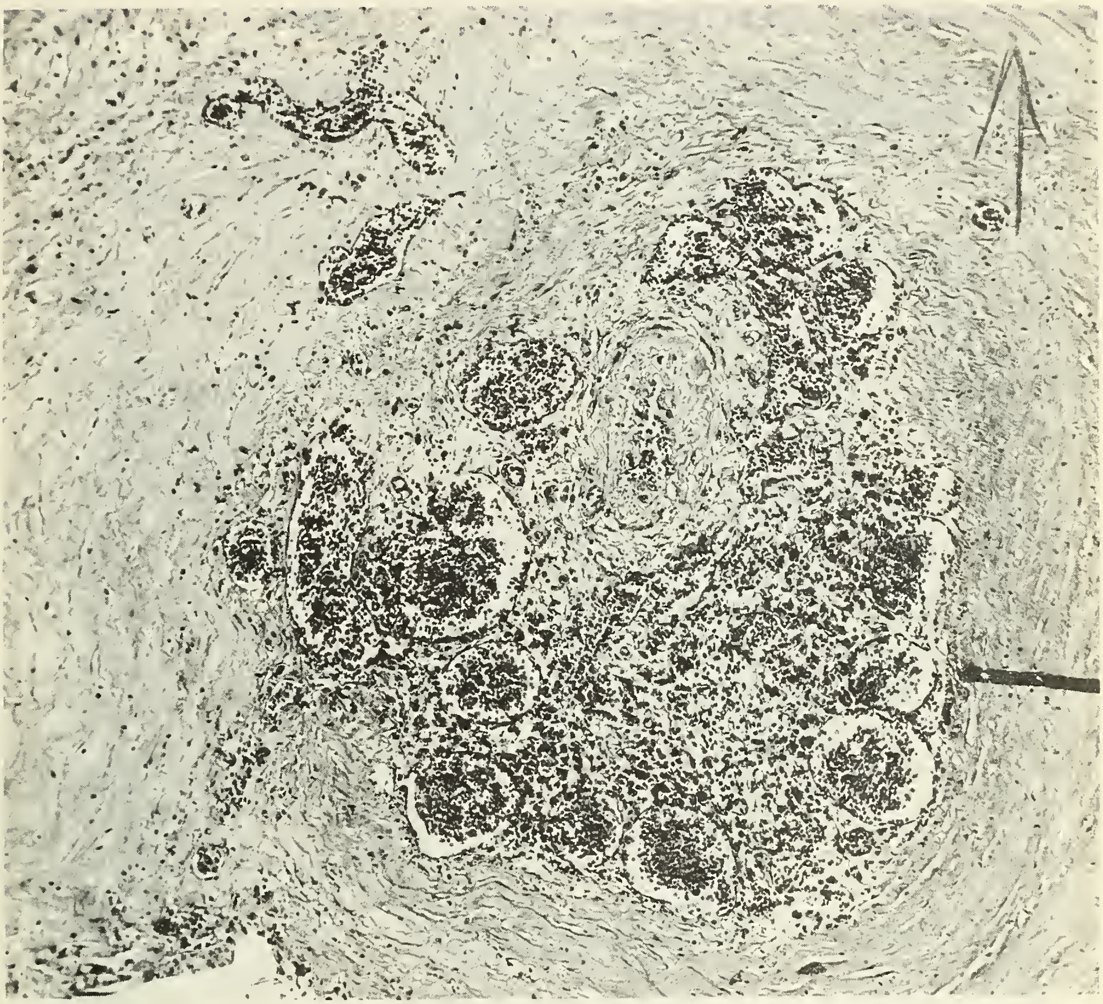
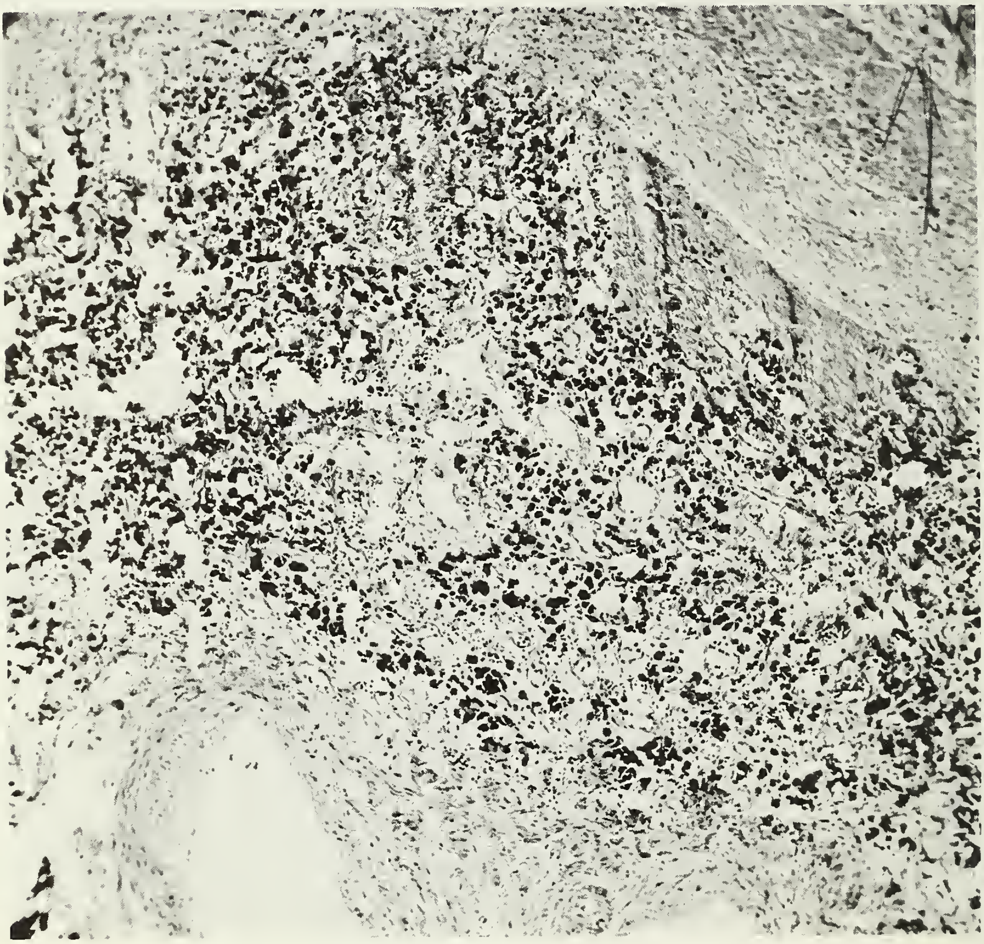


FIGURE 8

A portion of a coronary artery with hemosiderin deposition in an organized thrombus and contiguous atheroma. (H&E; X60) (AFIP Neg. 61-5724-2).



occurs acutely in an atherosclerotic plaque leading to arterial obstruction and clinical disease is not known. Further, the role that risk factors play in the etiology of the acute events in a plaque that lead to clinical disease is not known. Clarification of these two unknowns could do much to prevent or delay the onset of clinical disease.

There is almost no information available regarding the metabolism of fibrous plaques. Histochemical studies have generally shown a decrease in enzyme activities in plaques and complicated lesions compared to fatty streaks.[11] Studies of lipid composition of plaques compared to fatty streaks have shown the greatest differences to be an increase in the amount of free cholesterol relative to esterified cholesterol, and increased sphingomyelin in plaques.[11] Obviously, the information available is far too meager to be translated into an account of metabolic changes associated with or causative for plaque initiation and growth.

Unresolved Problems

The one overriding problem in atherosclerosis is that we do not as yet understand the basic mechanism underlying the development of the lesion, nor how various risk factors act to influence the progress of these lesions so as to bring about premature development of clinical disease. This lack of knowledge makes it difficult to develop a rational program of prevention and control.

There are several procedures for assessing the "severity" of atherosclerosis at autopsy, but none are generally accepted or utilized. "Severity" is a general term that incorporates into its meaning extent of lesions, type of lesions, and degree of lumen obstruction. If data collected in various centers are to be comparable we must have a uniform method for determining the severity of atherosclerosis.

Another problem is the difficulty in assessing the degree of atherosclerosis in a given patient during life. Presently the assessment of the severity of atherosclerosis and its rate of progression or regression can only be made with invasive methods such as coronary angiography. (See Section on Coronary Presymptomatic Atherosclerotic Disease.) There is a need for the development of safe noninvasive techniques to estimate the severity of atherosclerosis during life. Such methods would enable the detection of atherosclerosis at an earlier stage when it might be more responsive to intervention. These methods would also be valuable in accurately assessing the efficacy of intervention or therapy without endangering the patient's life.

The microscopic detection of ischemic tissue in specimens removed at autopsy is difficult until that point in time when cellular death and the reaction of inflammation are apparent. If a patient dies suddenly due to acute insufficiency of the blood supply to vital organs such as the heart or the brain, current microscopic techniques are not sensitive enough to register a change in the tissues. Thus, accurate diagnosis of the site of the lesion may be impossible. Hence, there is a need for further development of methods for early detection of ischemic tissue.[17]

Presently, collateral circulation channels can be demonstrated at autopsy by angiographic methods. There is need for development of methods for quantitating the amount of collateral circulation which will permit a prediction of its adequacy.

The role of hemodynamic forces in the genesis and localization of atherosclerotic lesions remains unknown, and needs to be evaluated.

The relation of fatty streaks to plaque formation is another unresolved problem. If it is true that some fatty streaks regress or remain stable while others progress to fibrous plaques, we must understand the reason for this variable behavior which quite obviously offers a logical point for prevention of plaque formation and disease.

Metabolism of normal arterial tissue and atherosclerotic lesions is incompletely understood. Metabolism is used here in the broadest sense of the word--oxygen consumption, energy generation, substrates oxidized, oxidative pathways, synthetic activity, permeability, and compositional changes. The atherosclerotic lesion is a reaction of the artery wall to injury; an understanding of this reaction has considerable potential for elucidating the mechanisms of localization of lesions and the differing susceptibilities of various arterial beds to lesions. This information could serve as a basis for the development of new preventive or therapeutic measures.

The cellular reaction of the arterial wall during lesion formation needs to be elucidated. Further studies of the origin of the cells in the lesion and the control of their metabolism with regard to lipids and connective tissue are needed.

The mechanism(s) of transport of lipids from the blood into the arterial wall is not understood.

The mechanisms by which fibrous plaques increase in mass were discussed above. Whether these are the only mechanisms is unknown and further the relative roles of these mechanisms is not known. The causes of arterial occlusion are at best incompletely understood and relate in part to the mechanisms of plaque growth. The role of hemodynamic forces in the causation of plaque complications is also in need of clarification.

There is need for continued development of experimental models especially for studies of plaque formation and growth, and of the relation of atherosclerosis to infarction and thrombosis.

Recommendations

1. There is an urgent need for continued and expanded support of basic investigations into the pathogenesis of the atherosclerotic lesion including the effect of hemodynamic forces, the relation of fatty streaks to plaque formation, the role of altered arterial wall metabolism and cellular reaction during lesion formation, the mechanism of transport of lipid across the arterial wall, and the mechanisms of growth of fibrous plaques.

2. The continued development of animal experimental models of the human disease should be supported.

3. A uniform method for determining the severity of atherosclerosis at autopsy needs to be established so that data collected at various research centers can be compared.

4. There is need for the development of safe noninvasive techniques for estimating the severity of atherosclerosis in the various arterial beds during life.

5. Methods for the early detection of ischemic tissue in autopsy specimens need further study.

6. A method of quantitating the adequacy of collateral circulation needs to be developed.

References

1. McGill HC Jr, Geer JC, Strong JP: Natural history of human atherosclerotic lesions. Atherosclerosis and Its Origin. Edited by M Sandler and GH Bourne. New York and London, Academic Press, 1963, pp 39-65.

2. McGill HC Jr, Editor: The geographic pathology of atherosclerosis. Lab Invest 18:463-653, 1968.

3. Mitchell JRA, Schwartz CJ: Arterial Disease. Oxford, Blackwell Scientific Publications, 1965.

4. Geer JC, McGill HC Jr: The evolution of the fatty streak. Atherosclerotic Vascular Disease (A Hahnemann Symposium). New York, Appleton-Century-Crofts, 1967, pp 8-22.

5. Sappington SW, Cook HS: Radial artery changes in comparison with those of the coronary and other arteries. Amer J Med Sci 192:822-839, 1936.

6. Westlake GE, Grundy SM, O'Neal RM: The effect of an atherogenic diet on pre-existing aortic intimal thickenings in old dogs. Exp Molec Path, Suppl 1:1-8, 1963.

7. Moreland AF, Clarkson TB, Lofland HB: Atherosclerosis in "miniature" swine. Arch Path 76:203-210, 1963.

8. Moss NS, Benditt EP: The ultrastructure of spontaneous and experimentally induced arterial lesions; III. The cholesterol-induced lesions and the effect of a cholesterol and oil diet on the pre-existing spontaneous plaque in the chicken aorta. Lab Invest 23:521-535, 1970.

9. Lofland HB, Clarkson TB: The bi-directional transfer of cholesterol in normal aorta, fatty streaks, and atheromatous plaques. Proc Soc Exp Biol Med 133:1-8, 1970.

10. Adams CWM, Bayliss OB: The relationship between diffuse intimal thickening, medial enzyme failure and intimal lipid deposition in various human arteries. J Atheroscler Res 10:327-339, 1969.

11. Geer JC, Paganamala RV, Newman HAI, et al: Mural metabolism. Atherosclerosis: Proceedings of the Second International Symposium. Edited by RJ Jones. New York-Heidelberg-Berlin, Springer-Verlag, 1970, pp 6-12.

12. Dayton S, Hashimoto S: Recent advances in molecular pathology: A review; Cholesterol flux and metabolism in arterial tissue and in atheromata. Exp Molec Path 13: p253-268, 1970.

13. Wissler RW: Editorial. The arterial medial cell, smooth muscle, or multifunctional mesenchyme? Circulation 36:1-4, 1967.

14. Anitschkow N: Experimental Arteriosclerosis in animals. Arteriosclerosis, A Survey of the Problem. Edited by EV Cowdry. New York, The MacMillan Co, 1933, pp 271-322.

15. Armstrong ML, Warner ED, Connor WE: Regression of coronary atheromatosis in rhesus monkeys. Circ Res 27:59-67, 1970.

16. Constantinides P: Experimental atherosclerosis. Amsterdam-London-New York, Elsevier Pub Co, 1965, pp 1-88.

17. Lee JT, Holley KE, Kampa WR, et al: New histochemical method for morphologic diagnosis of early stages of myocardial ischemia. Mayo Clin Proc 46:319-327, 1971.

B. THROMBOSIS

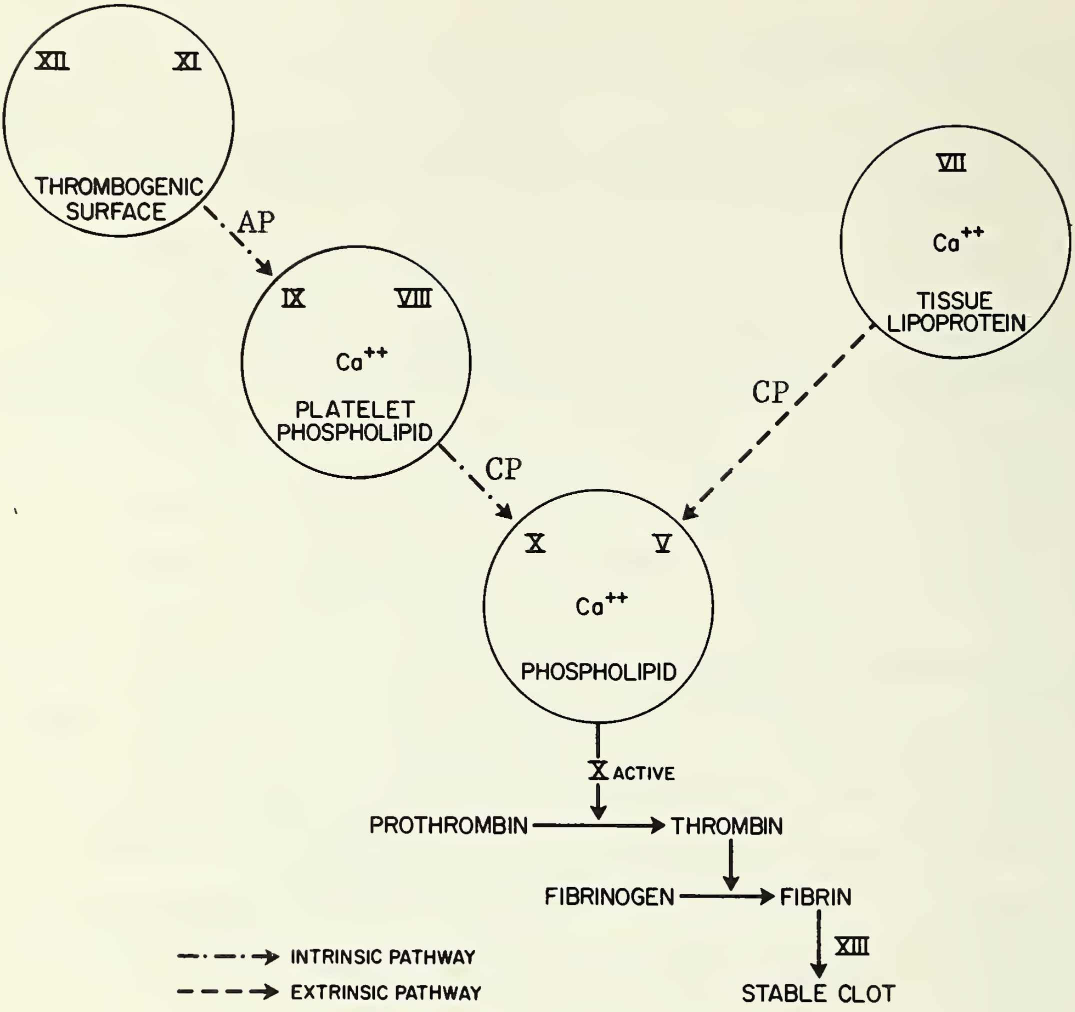
Current State of Knowledge

Thrombosis is intimately related to atherogenesis. It not only contributes to the progression of atherosclerotic lesions but also is responsible for many of the clinical complications of atherosclerosis. Thrombosis may result in occlusion of the arterial lumen causing acute myocardial infarction. Thrombi overlying atherosclerotic lesions, as in the aorta, may become dislodged and by embolism cause arterial occlusion and infarction in distant body sites. If the thrombotic process could be halted or reversed, some of the serious consequences of atherosclerosis might well be reduced.

Basic Mechanisms of Thrombosis. Three main biologic mechanisms or functions of the blood are operative in thrombosis. They are: 1) Fibrin coagulation;[1,2] 2) platelet adhesion and aggregation;[3,4] and 3) decreased fibrinolysis.[5] All of these mechanisms are complicated, but once understood, they become a potential advantage in the control of thrombosis, since they offer so many points at which the individual systems may be altered to reduce the tendency to thrombosis.

Of the three mechanisms, knowledge of fibrin coagulation is most advanced. Fibrin coagulation involves a series of enzyme activations of procoagulant proteins in the blood plasma, in the presence of tissue and cellular components, along with calcium. These steps are diagrammed in Figure 1. The reaction may proceed along either of two parallel routes, the so-called intrinsic and extrinsic pathways, which finally result in activated Stuart factor (Factor X), and finally thrombin. The final stages of clotting, the conversion of of fibrinogen to the fibrin clot, and its stabilization with Factor XIII are

FIGURE 1



Schema of Biochemical Pathways in Formation of Fibrin Thrombus

The upper part of the schema illustrates the two separate tracks along which clotting can be initiated, the intrinsic pathway (left side) and the extrinsic pathway (right side).

The intrinsic pathway has two action centers (circles) in the blood. The first (top, left) is the activation center, in which two trace plasma protein procoagulants, Factors XII and XI, interact with a thrombogenic surface. Activation product (AP) is formed. It triggers the anti-hemophilia center (circle) in which the two antihemophilia factors of plasma, VIII and IX, with calcium and phospholipid micelles from blood platelets, form a conversion product (CP) for the next step.

Legend for Figure 1, continued

The extrinsic pathway has a single action center (top circle, right) in which lipoprotein derived from damaged tissue (i.e., extrinsic to the blood) reacts with calcium and a trace plasma protein, Factor VII, to form a second conversion product (CP) that can also activate the next step.

The common pathway (center circle), triggered by the conversion product of either the intrinsic or extrinsic pathway, results in the interaction of two plasma protein procoagulants, Factors V and X, calcium and phospholipid micelles to yield active Factor X, the key enzyme for conversion of prothrombin to thrombin.

Thrombin brings about the transformation of soluble fibrinogen to the insoluble fibrin of the thrombus. Still another plasma protein, Factor XIII, is required for cross-linking the fibrin strands to form the stable thrombus.

best understood in molecular terms. There is a system of inhibitors in the plasma which causes inactivation of the procoagulant enzymes and helps to provide a physiological control mechanism for maintaining the fluidity of the blood. This homeostasis may be disturbed in many ways. For example, there are families with thrombophilia in which one of the inhibitors, antithrombin III, is deficient.[6] The affected members are prone to have recurrent thrombo-embolic episodes with premature deaths from this cause.

Platelet aggregation and adhesion appear to be even more important than fibrin clotting in the initiation of thrombosis. In cardiac and arterial thrombi, platelets may contribute significantly to the growth and total mass of the thrombus. Platelet aggregation or cellular clotting appears to be inextricably tied up with fibrin clotting, both biochemically and by furnishing surfaces and structures to which the fibrin fibrils are attached. The platelet is being studied intensively as a cell. Much the same as with other cells, there are problems relating to cellular respiration, energy metabolism, cell membranes, and contractility, as well as intercellular organization by adherence to other platelets, other cells, and various surfaces. Alterations in the cell membrane may be the most important aspect of platelet change in that it may be the attribute that permits platelets to be actively incorporated into a growing thrombus. The antithrombotic drugs which inhibit platelet aggregation could act by stabilizing platelet membranes.[7]

Fibrinolysis is considered part of the biological repair mechanism in that excess fibrin can be removed enzymatically. In fibrinolysis, as in the clotting sequence, there is an interplay of tissue components and trace proteins of the plasma. If fibrinolysis operates directly to remove fibrin, new growth of tissue through organization of the thrombus is obviated. On the other hand, failure of the fibrinolytic system could accelerate the progress of arteriosclerosis. Dissemination of digestion products of fibrin are potential markers for the existence of a thrombus.

In addition to these three basic biologic systems, there are two other major facets of the thrombotic process: 1) Injury to the vascular wall;[8] and 2) alteration in blood flow.[9] Injury to the vessel wall, particularly to the endothelial lining, may be the event which triggers the thrombotic process. An important property of normal endothelium is that it is nonthrombogenic and allows the blood to remain fluid, regardless of the flow rate of the blood. As opposed to the nonthrombogenic character of the endothelium, the deeper structures of the vessel wall are thrombogenic. This is particularly the case with the basement membrane and the collagenous and possibly other tissue components, both normal and abnormal. Endothelial damage may cause exposure of the collagen in a fibrous plaque or deposited lipids to the blood interface resulting in thrombosis.

Altered circulatory dynamics appear to contribute to thrombosis only after there has been some alteration in the clotting system of the blood or a change in the contours of the vascular wall. The thrombosis-promoting character of stasis has been recognized for over a century, since the time of Virchow. It would appear that altered rheology abets the thrombotic process mainly in two ways: by amplifying the enzymatic and cellular reactions important in thrombogenesis, and by producing further injury to the vessel wall. In regard to amplification, stasis appears to act in part by preventing dilution of thrombin and other procoagulant enzymes that contribute to cellular and fibrin clotting. The increase in viscosity that occurs as flow rate decreases may partially counterbalance this effect if it reduces molecular and cellular collisions in the blood. Turbulence and the related loss of laminar flow could likewise result in amplification of some reactions; this is perhaps analogous to accelerating a chemical reaction in a test tube by stirring vigorously with a glass rod. Cellular injury to the vessel wall may be extended by rheologic alterations associated with thrombi. Hypertension may contribute to endothelial damage, particularly in the thin part of the cells at their junctions. Narrowing of a vessel by an atherosclerotic plaque or a thrombus may result in shear forces and stagnation points which may further injure the vessel wall. Extension of the cellular injury, in effect, may create a vicious cycle, providing new foci for thrombus formation on the adjacent vascular surfaces, and still further alterations in blood flow.

Thrombosis and the Genesis of Atherosclerotic Lesions. Thrombi have been considered to play a role in each stage of the development of atherosclerotic lesions.

Data relating thrombosis to the fatty streak are fragmentary. It has been suggested that platelet microthrombi on the vessel wall may contribute in two ways: 1) Platelets, when activated, release many cellular components and enzymes which may directly injure the vessel wall.[4] The resultant altered permeability characteristics of the endothelium could be the primary event in the genesis of the fatty streak. 2) Platelets are rich in lipids. When platelet aggregates are incorporated into the subendothelial layer, they are phagocytosed to yield foam cells. In addition, fibrin has been demonstrated in fatty streaks both by labelled antifibrin antibodies and by electron microscopy, but it is ordinarily inconspicuous.

One of the major theories of the development and growth of the fibrous plaque is the encrustation hypothesis.[10] The fibrous plaque often has a mosaic pattern, suggesting successive crops of thrombi which have become organized.[11] There is no doubt that the thrombotic complication of atherosclerosis is one of the most important pathologic events, often catastrophic, in the natural history of the disease.

Identification of the thrombosis-prone individual. Many studies have shown that coagulation and fibrinolytic factors are altered in patients with peripheral atherosclerosis, ischemic heart disease, and stroke. Elevations of plasma fibrinogen and the plasma procoagulants, Factors V, VII, VIII, IX, and X,[5,12-15] have been reported. Likewise, shortening of several standard clotting time tests, including the prothrombin time and the partial thromboplastin time, have been found in such patients.

Reduction in inhibitors of coagulation, particularly antithrombin III, has been observed. Thrombocytosis has been mentioned. Increased platelet stickiness has likewise been reported, but methodology is not yet well standardized in this field. Reduction in fibrinolytic activity, including elevation in antiplasmin and anti-urokinase inhibitor titers, has been found in patients who have had myocardial infarction when compared to healthy age-matched controls. These data strongly suggest that tests on the blood can be developed that would be related to thrombosis, either impending or incipient, and indicate the need for further developmental and epidemiological studies.

Hypercoagulable states and risk factors for thrombosis. It is important to recognize that the term hypercoagulability is used in two separate senses, both related to a change in the circulating blood which is indicative of altered coagulation.[14] One use of the term is for an antecedent condition which enhances the thrombotic potential. In this state the total clotting apparatus has been modified, as by increased levels of procoagulants or diminished inhibitors of coagulation. Once the mechanism is triggered there may be accelerated clotting, with thrombosis occurring at sites of arteriosclerotic lesions, as well as in the veins, along with systemic changes in the blood. Elevations in the levels of normal constituents of the blood, e.g. antihemophilic factors, would be an indicator of this state.

The other use of the term hypercoagulability is for the altered state of the circulating blood coexisting with diffuse intravascular clotting or with local thrombotic events. In diffuse intravascular clotting, hypercoagulability is a transitory state, frequently leading to hypocoagulability.[16] In the case of coexisting thrombi, coagulants or products of coagulation would leak from the thrombus, and would be detectable in the circulating blood. Alterations in the levels of normal constituents of the blood combined with the presence of activated or altered products of coagulation or fibrinolysis, including pathologic changes in the formed elements such as helmet-shaped red cells, would be indicators of this type of hypercoagulable state.

It may well be that systemic changes in the blood precede thrombotic complications of atherosclerosis. However, the triggering mechanism is not known. Furthermore, it is not known whether risk factors of atherosclerosis result in a hypercoagulable state. The possible relationship of cigarette smoking to increased platelet adhesiveness has been cited in this connection. Hormones, both epinephrine and the estrogens, may cause a rise in the plasma level of antihemophilic factor.[17,18]

Many other ways in which known risk factors might operate to cause thrombosis have been described. The thrombogenic effect of certain complex lipids is an example.

Prevention and therapy of thrombotic complications of atherosclerosis. The thrombo-atherosclerosis field offers many opportunities for controlled manipulations of basic pathophysiologic mechanisms and hence for specific therapy and prevention of the thrombotic complications of this disease.

In some cases the manipulations are relatively imprecise, as with the use of indirect anticoagulants such as warfarin. In other cases remarkably precise bioengineering is possible, as would be the case with the administration of plasma concentrates of antithrombin III in patients with a deficiency of this factor.

Many actual and proposed procedures for the management of thrombotic disorders are indicated in Table I. Listed are modifications of biologic mechanisms which, if brought about, could correct at least partially the basis for thrombotic disorders. The agents represent: 1) Old and well tried products, such as warfarin and heparin; 2) relatively new products in the clinical testing phase, such as coagulating snake venoms and urokinase; and 3) new products incompletely developed or in the preliminary testing phase, such as platelet anti-aggregating drugs. By vigorous development along pathophysiologic lines it can be anticipated that continuing advances

TABLE I

CONTROL OF THROMBOTIC DISORDERS BY MODIFYING UNDERLYING PATHOPHYSIOLOGIC MECHANISMS

MODIFICATION	AGENT
COAGULATION MECHANISMS	
1. Reduce fibrinogen	Coagulating snake venoms Staphylocoagulase
2. Reduce fibrinogen function	Fibrinogen split products Cellular cationic proteins
3. Prevent thrombinemia	Thrombin-blockers a) Hirudin-like compounds b) Enzyme inhibitors
4. Metabolically block procoagulant synthesis	Warfarin, dicumarol, etc.
5. Directly block procoagulant action	Heparin Heparinoids Enzyme inhibitors Cellular cationic proteins
6. Increase natural clotting inhibitors	Plasma concentrates: Antithrombin III
7. Prevent clot stabilization	Enzyme inhibitors (anti-Factor XIII)
PLATELET MECHANISMS	
1. Inhibit platelet function	
a. Extrinsic to platelet	
(1) Reduce fibrinogen cofactor	Coagulating snake venoms
(2) Reduce thrombin function	Fibrinogen split products Enzyme inhibitors
(3) Reduce surface function	Dextrans
b. Intrinsic to platelet	
(1) Alter membrane reactivity and release reactions	Drugs, such as aspirin, pyrazoles, local anesthetics, antihistamines, anti-epinephrine drugs, prostaglandins, theophylline

Table 1, continued

2. Reduce number of circulating platelets	
FIBRINOLYTIC MECHANISMS	
1. Increase fibrinolysis (thrombolysis)	Streptokinase Urokinase Drugs, such as phenformin Direct enzymatic agents
2. Reduce inhibitors of plasmin	
SURFACE FACTORS: FLUID MECHANICS	
1. Restore vascular non-thrombogenicity	Dextran
2. Use hypo-thrombogenic prostheses	Heparin-coating Appropriate polymers
3. Improve blood flow	Dextrans Exercise (?) Drugs (?) Others

will be made, with better and more specific management of the thrombotic disorders in the immediate years ahead.

Unresolved Problems

In spite of the tremendous advances that have been made in the field of blood coagulation and fibrinolysis, the application of these findings to thrombosis and arteriosclerosis are at an embryonic stage. This appears to be due to gaps in knowledge in regard to physiologic mechanisms and to lack of definitive knowledge in the pathogenesis and histogenesis of atherosclerotic lesions and their thrombotic complications. Until this basic knowledge is further advanced, applications of this body of information to the health problems created by arteriosclerosis will need to be empirical.

In regard to the role of coagulation mechanisms in the pathogenesis of the fatty streak and its conversion to the fibrous plaque, the lack of suitable animal models is a significant handicap. The extent to which the thrombotic process may be a mechanistic pathway by which different risk factors may express themselves is completely unresolved, and needs to be established.

In regard to the early diagnosis of thrombotic complications of atherosclerosis, the value of newer laboratory, radiologic, and other noninvasive techniques has not been adequately explored. New and novel procedures need to be sought.

The role of anticoagulant therapy in coronary artery disease is not yet fully resolved. The place of newer drugs such as platelet anti-aggregating and thrombolytic agents in the therapy of complications of atherosclerosis needs definition.

With the potential involvement of the thrombotic process at all stages of the natural history of the atherosclerotic diseases, and the multiple points at which the coagulation process can be entered to inhibit its action, intensive basic research in the thrombotic process and its underlying physiologic mechanisms could yield keys to effective prevention.

While much basic information is still lacking, particularly in the platelet field, it is believed that a planned approach to some segments of the thrombotic process would now be more profitable than in the past. Both programmed research in applied and developmental problems and individual and group research to acquire basic information will be needed to advance the field fully in the near future.

Recommendations

1. The Task Force recommends that there be no diminution in funds for the support of investigator initiated basic research in thrombosis. Attention should be given to specific areas of basic research that would appear to provide a sounder base of knowledge for applications in prevention and therapy. The following is a partial list of subject areas developed by the Thrombosis Panel (See Appendix B) of the Task Force as needing urgent attention: vascular endothelium and supporting basement membrane; mechanochemistry and surface chemistry as related to the clotting process; fibrin coagulation mechanisms including biochemistry of procoagulants and inhibitors, biosynthesis of procoagulants, role of hormones in clotting, coagulation immunology and immunoassays, and syndrome of diffuse intravascular coagulation; platelets, including cell biology and nature of platelet aggregation and adhesion; fibrinolysis; and animal models for thrombo-atherosclerosis.

2. Clinical laboratory procedures need to be developed for the detection of hypercoagulability and thrombotic tendency. These procedures would be used to establish "coagulation and fibrinolytic profiles" in patients for the purpose of identifying thrombosis-prone individuals and those with occult thrombosis. If the results are to be applied for screening populations, relatively inexpensive automated procedures amenable to computerization will be required. Suggested areas of study are: Development of an automated battery of tests with appropriate quality control which include common procedures such as the partial thromboplastin time, as well as procedures for antithrombin III assays, and tests for fibrin degradation products in plasma or serum; new methodology for determining platelet adhesion and aggregation, and related platelet functions; and evaluation of morphologic alterations in platelets, leucocytes, and erythrocytes as indicators of thrombosis.

3. Further clinical trials of anticoagulant drugs are recommended. The direct anticoagulant, heparin, and the indirect anticoagulants, warfarin and related compounds, acting as anti-vitamin K, have been studied most extensively. Debate continues as to the long-term value of these agents in arteriosclerosis. Of the newer agents, coagulating enzymes derived from snake venom appear most promising. It is recommended that attention be given to clinical trials of these newer venom derivatives both alone and in conjunction with the older anticoagulants.

4. Clinical trials are needed to determine the preventive and therapeutic value of platelet anti-aggregating drugs. Only a limited number of drugs are available as possible candidates for clinical trials; one of these is

aspirin. Limited clinical trials have been conducted, but more definitive data are needed. Consideration of the feasibility of clinical trials of aspirin in the secondary prevention of myocardial infarction and in patients with transient ischemic attacks (TIA) is indicated. As newer platelet anti-aggregating agents are developed and toxicologic studies are completed, clinical trials of these agents should be conducted. Certain lower molecular weight dextrans appear to coat platelets as well as the endothelium, and show promise in preventing platelet thrombus formation. A clinical trial of dextran in TIA or other clinical conditions associated with arterial thrombosis should be considered.

5. Additional clinical trials of thrombolytic drugs are recommended. The agents streptokinase and urokinase are well established, and successful clinical trials in certain thrombotic states have indicated their usefulness. However, additional studies need to be done to determine their role in resolving thrombotic complications of atherosclerosis such as coronary thrombosis, both alone and in combination with anticoagulant and platelet anti-aggregating drugs.

References

1. Brinkhous KM, Roberts HR, Hinnom S, et al; Editors: Fibrinogen: structural, metabolic and pathophysiologic aspects. Thromb Diath Haemorrh Suppl 39, 1970

2. Stormorken H, Owren PA: Physiopathology of hemostasis. Seminars Hemat 8:3-29, 1971

3. Brinkhous KM, Shermer RW, Editors: The Platelet. Baltimore, Williams and Wilkins, 1971

4. Mustard JF, Packham MA: Factors influencing platelet function: adhesion, release, and aggregation. Pharmacol Rev 22:97-187, 1970

5. Nilsson IM, Krook H, Sternby NH, et al: Severe thrombotic disease in a young man with bone marrow and skeletal changes and a high content of an inhibitor in the fibrinolytic system. Acta Med Scand 169:323-337, 1961

6. Egeberg O: Inherited antithrombin deficiency causing thrombophilia. Thromb Diath Haemorrh 13:516-530, 1965

7. Lacefield WB, Hermann RG, Mills J, et al: Inhibitors of blood platelet aggregation. 1. Biphenylyloxyalkamines. J Med Chem 14:133-135, 1971

8. Brinkhous KM, Rodman NF, Hinnom S (Editors): Vascular factors and thrombosis. Thromb Diath Haemorrh Suppl 40, 1970

9. Sherry S, Brinkhous KM, Genton E, et al (Editors): Thrombosis. Washington DC, National Academy of Sciences, 1969, pp 461-495

10. French JE: Atherogenesis and thrombosis. Seminars Hemat 8:84-94, 1971

11. Constantinides P: From personal communication to Arteriosclerosis Task Force, 1970, entitled "Contributions of experimental work to elucidation of pathogenesis and determination of best treatment for atherosclerosis"

12. Ettinger MG, Kusonoki R, Fujishima H: Stroke: US and Japan, Blood Coagulation Studies. Geriatrics 24:116-125, 1969

13. Fearnley GR: Fibrinolysis and its pharmacological enhancement in occlusive vascular disease. Advances Cardiol 4:211-284, 1970

14. Penick GD, Roberts HR: Intravascular clotting: focal and systematic. Int Rev Exp Path 3:269-328, 1964

15. Pilgerman LO: Relation of plasma fibrinogen concentration changes to human arteriosclerosis. J Appl Physiol 16:660-664, 1961

16. Deykin D: The clinical challenge of disseminated intravascular coagulation. New Eng J Med 283:636-644, 1970

17. Barrow EM, Dejanov II, Ingram GIC, et al: The rise in factor VIII after administration of adrenalin. Coagulation 2:203-211, 1969

18. Crowell EB Jr, Clatanoff DV, Kiekhofer W: The effect of oral contraceptives on factor VIII levels. J Lab Clin Med 77:551-557, 1971

III. RISK FACTORS

Epidemiological studies have demonstrated associations between the development of the clinical manifestations of arteriosclerosis and certain biochemical, physiological, and environmental factors. By definition the presence of one or more of these factors in an individual will increase the risk of arteriosclerosis and its complications. To a considerable degree, these associations have been determined from the study carried out in Framingham, Massachusetts by the National Heart and Lung Institute. In this study about 5,000 men and women, constituting a reasonably representative sample of the adult population of the town, have been followed biennially since 1949 for the development of initial attacks of coronary heart disease (angina pectoris, myocardial infarction, "coronary insufficiency," and sudden death*).

From this and other studies the following factors have been identified with risk from coronary heart disease:

1. Age
2. Male sex
3. Elevated serum lipids
4. Hypertension
5. Cigarette smoking
6. Impaired glucose tolerance (diabetes mellitus)
7. Obesity

---

* Sudden unexpected death occurring within less than one hour of onset of symptoms in persons not suffering from potentially lethal diseases and with medical history suggesting no other causes.

8. Physical inactivity
9. Personality and behavior
10. Family history (genetics)
11. Gout
12. Hardness of drinking water

It is possible on the basis of these risk factors to identify persons especially susceptible to the development of the clinical complications of atherosclerosis and to develop programs of primary prevention especially for children and young adults. Such preventive measures offer great promise of reducing the high mortality from complications of atherosclerosis. They may also be of value in reducing the threat of recurrent clinical episodes, i.e., secondary prevention, or postponing their onset.

The strongest associations are with elevated serum lipids, hypertension, and cigarette smoking and these will be discussed in detail in subsequent sections as well as certain of the other risk factors that are important or of special interest. Certain of these factors are weakly related to risk, and their significance is by no means certain. It should be noted that an appreciable number of patients with arteriosclerosis do not exhibit any of these risk factors suggesting that there are, as yet, undiscovered factors involved in atherogenesis.

Age and Sex. The incidence of arteriosclerosis increases with age, as shown in the section on Magnitude of the Problem (Appendix C). The death rate in white males is about 10 per 100,000 at age 25-34 whereas at age 55-64 it is nearly 1,000 per 100,000. Age may be an expression of the time required for the development of lesions. It may also reflect the duration of exposure to other risk factors.

Male sex is an important risk factor. At ages 35-44 the death rate from coronary heart disease in white males is 6.1 times that of females. At age 65-74 the rates are 2.2 times higher in males. In non-whites the sex difference is less marked. The reasons for the observed sex difference in risk are not understood. In 1952[1] it was shown that administration of estrogens to males who had survived myocardial infarction resulted in a decrease in ß-lipoproteins and a rise in α-lipoproteins. Therefore it appeared likely that the relatively low incidence of coronary disease in younger females might be related to the level of female sex hormones. However, in subsequent studies[2] administration of estrogens to women was found to increase rather than decrease the concentrations of very low density lipoproteins (VLDL). Since it is probable that these lipoproteins are also atherogenic, it would seem unlikely that the effect of estrogens on serum lipoproteins explains the sex difference in incidence. Furthermore, it is not clearly evident that the incidence of arteriosclerosis in females rises coincident with the menopause as has frequently been stated.[3]

Gout. Subjects in the Framingham Study with elevated levels of uric acid had an increased incidence of coronary heart disease. This was apparent in patients with uric acid levels of 6.9 mg. per 100 ml. and above. The reasons for this association are not known. It is of interest that there are numerous case reports showing associations between levels of serum cholesterol and uric acid.

Hardness of Drinking Water. In 1960 Schroeder[4] reported that there was a negative correlation between water hardness and cardiovascular mortality (the softer the water, the higher the mortality.) In England and Wales[5], similar results were found. Subsequent studies have tended to exclude water hardness per se, as well as calcium and magnesium as being involved on other than a chance basis. The possibility of there being other water factors remains. Schroeder[6] has suggested that cadmium found in galvanized iron pipes may be dissolved by soft, acidic surface water. However, there is still considerable uncertainty as to the validity of these correlations and much additional work remains to be done on this subject.

References

1. Barr DP, Russ EM, Eder HA: Influence of estrogens on lipoproteins in atherosclerosis. Trans Ass Amer Physicians 65:102-113, 1952

2. Furman RH, Alaupovic P, Howard RP: Effects of androgens and estrogens on serum lipids and the composition and concentration of serum lipoproteins in normolipemic and hyperlipidemic states. Progr Biochem Pharmacol 2:215-249, 1967

3. Furman RH: Are gonadal hormones (estrogens and androgens) of significance in the development of ischemic heart disease: Ann NY Acad Sci 149:822-833, 1968

4. Schroeder HA: Relation between mortality from cardiovascular disease and treated water supplies: Variations in states and 163 largest municipalities of the United States. JAMA 172:1902-1908, 1960

5. Morris JN, Crawford MD, Heady JA: Hardness of local water-supplies and mortality from cardiovascular disease in the county boroughs of England and Wales. Lancet 1:860-862, 1961

6. Schroeder HA: The water factor. New Eng J Med 280:836-838, 1969

A. LIPIDS AND LIPOPROTEINS

1. Relationship Between Arteriosclerosis and Lipids and Lipoproteins

Current State of Knowledge

The relationship between arteriosclerosis and lipid metabolism derives from the following information: 1) the lipid content of the atherosclerotic lesion; 2) the production of atherosclerotic lesions in animals by measures that increase levels of serum lipids; 3) serum lipid levels in patients who have clinical evidence of arteriosclerosis; 4) the occurrence of arteriosclerosis in patients with hyperlipoproteinemia; 5) prospective studies relating the occurrence of arteriosclerosis to serum lipid levels; and 6) epidemiologic studies carried out in populations with differing levels of serum lipids.

Serum cholesterol concentrations above 200 mg/100 ml are rarely found in humans or in animals except for man in affluent society. Even in those animal species in which serum cholesterol is relatively high, the cholesterol is present mostly in the α-lipoproteins which are not atherogenic. In the United States, on the other hand, the average serum cholesterol concentration for men aged 50-59 is 240 mg/100 ml and most of the cholesterol is present in beta and prebeta lipoproteins which have been shown to be associated with atherogenesis. These lipoproteins are also found in very high concentrations in patients with severe premature arteriosclerosis and in animals fed atherogenic diets.

Studies in Animals. In 1913 Anitschkow[1] demonstrated that arterial lesions containing lipid could be produced in rabbits by feeding diets high in cholesterol. The cholesterol in the arterial lesions, as in blood serum, is present both in the free and the esterified forms. In addition to cholesterol, excessive phospholipid is also found in the fatty streak and atheroma.[2,3] Although the cholesterol in atheromatous lesions appears to be entirely derived from the circulating cholesterol, experiments in animals and in man indicate that the phospholipids are synthesized largely in the arterial wall.[3] Since Anitschkow, similar experiments have been performed in many species.[4] In the chicken, like the rabbit, arterial lesions occur after cholesterol feeding whereas in other species, like the dog and the rat, it is necessary to suppress thyroid function to generate the lesions. Recently Wissler et al. fed diets resembling usual American diets to Rhesus monkeys and found lesions similar to those seen in humans. There was a close correlation between serum cholesterol levels and the severity of the lesions. In another study it was demonstrated that in Rhesus monkeys fed diets containing cholesterol, serum cholesterol increases and arterial lesions appear.[5] When the monkeys were returned to diets low in cholesterol, serum cholesterol decreased and the lesions decreased in size.

Studies in Man. Since the early 1940's, numerous studies have shown that in groups of patients who have coronary heart disease the mean serum cholesterol is elevated although many of the individual patients have values well within the normal range. These differences are especially marked in younger individuals with coronary heart disease. Subsequently, it was demonstrated[6] that serum triglyceride concentrations are also higher in patients with coronary heart disease.

It is now recognized that virtually all of the lipids in plasma are transported as constituents of lipoproteins. Four classes of lipoproteins are present in plasma: the chylomicrons, the very low density lipoproteins (VLDL) with pre-β-mobility by electrophoresis, the low density lipoproteins (LDL) with β-mobility, and high density lipoproteins (HDL) with α-mobility. Recently Fredrickson et al.[7] have attempted to classify the various types of hyperlipidemia in terms of lipoprotein patterns. This classification (as recently modified)[8] is described in Table 1. Patients with type II lipoprotein pattern with elevated levels of LDL have a high incidence of coronary heart disease. In certain patients in whom both parents have elevated levels of LDL, the so-called homozygous type II, the levels of LDL are extremely high and myocardial infarction occurs even in young children. Individuals with elevated levels of VLDL also appear to have an increased incidence of coronary heart disease, although this has not yet been adequately studied.[9]

The levels of the various lipoproteins in the serum are determined by the dynamic equilibrium between formation and degradation. Control of the system may, in principle, derive from the biosynthetic or from the degradative side. Recent studies with the very low density lipoproteins have shown that synthesis in the liver is a stepwise process consisting of synthesis of the protein portion of the lipoprotein[10], which probably occurs in the rough endoplasmic reticulum, the combination of protein with lipid and the accumulation of lipoproteins which occurs in the Golgi apparatus.[11] Regulation of the rate of lipoprotein formation can occur at the level of synthesis of the specific protein or lipid or at a later stage, such as release of the lipoprotein into the plasma. Recently, a number

TABLE 1

HYPERLIPOPROTEINEMIA

TYPE & EST. PREVALENCE	CHOLESTEROL LEVEL	TRIGLYCERIDE LEVEL	CORONARY DISEASE RISK
I RARE	↑	⬆	↑
II COMMON	↑	IIa NORMAL IIb ↑	⬆
III RARE	↑	↑	⬆
IV COMMON	↑ OR NORMAL	↑	↑
V FAIRLY COMMON	↑ OR NORMAL	⬆	↑

of workers have shown that the protein portion of the various lipoproteins consists of a mixture of proteins some of which are present in different lipoprotein classes.[12] It is apparent that the synthesis of any one of these may be a determinant for the formation of entire classes of lipoproteins. This indeed has recently been demonstrated in the genetic disease familial abetalipoproteinemia in which one of the constituent proteins of the lipoproteins has been found to be absent. Preliminary studies have identified several instances in which abnormally high serum lipoprotein concentrations are due to disturbances in the degradative pathways. Little is known about the mechanisms whereby the protein portion of the lipoprotein is removed from the bloodstream and subsequently metabolized. Studies of kinetics of the removal of lipoproteins from the plasma and studies of the control of cholesterol excretion and degradation by liver and other organs will, undoubtedly, lead to an understanding of these processes.[13]

International epidemiological surveys[14] and prospective studies, such as the Framingham Study[15] and the study carried out in Albany,[16] have shown that the incidence of coronary heart disease increases with the level of serum cholesterol. The data from the Framingham Study show that individuals in the upper quartile of serum cholesterol concentrations have a much higher risk of myocardial infarction than do individuals in the lower quartile. This relationship is stronger in younger persons than in older persons. It is important to emphasize that there does not appear to be a critical level of serum lipids for the development of coronary heart disease. The risk appears to rise in proportion to the antecedent serum cholesterol concentration from the lowest to highest values recorded in this population sample. These data indicate that the risk of coronary heart disease depends upon the degree of serum cholesterol elevation (Figure 1).

Unresolved Problems

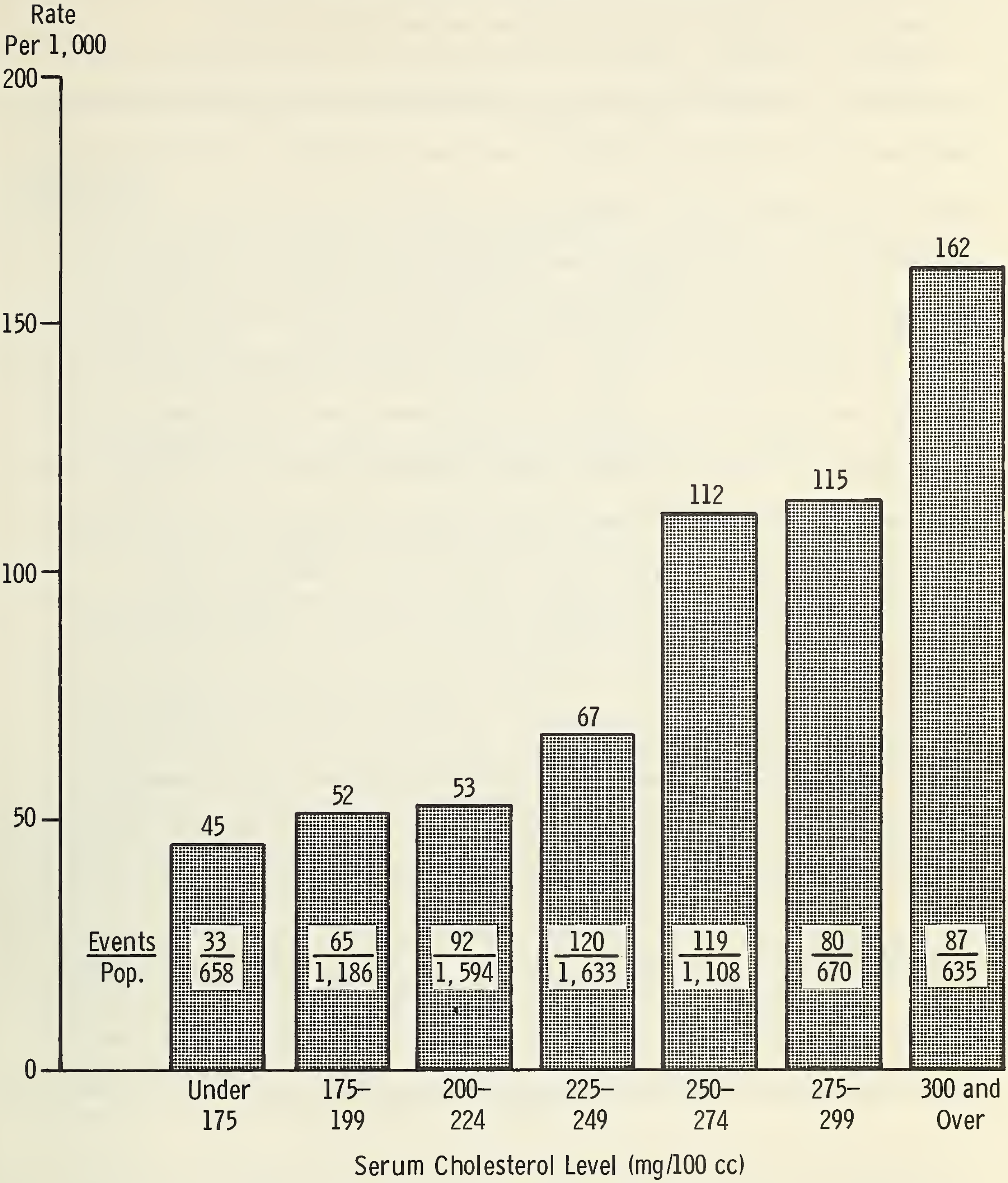
In many experimental animals subjected to atherogenic diets, the accumulation of lipids in the aorta and in the coronary arteries mimic that found in the arterial fatty streaks observed in man. However, the progression of fatty lesions to the more advanced fibrotic plaques and to clinical manifestations of disease, which is assumed to take place in man, is seen only rarely in the available animal models.[4] Whether this failure is the result of differences in the structure of the arterial wall or in the nature of the lipid-protein complexes in the bloodstream is, as yet, not known.[7]

The mechanisms whereby the various lipid and lipoprotein concentrations are maintained at greatly different levels in the blood of different individuals are poorly understood.[7] In the sequence of cholesterol biosynthesis, one early control point has been demonstrated, but there are indications that controls in biosynthesis at later stages of synthesis also exist. The difficulties in studying the later stages are related to the insolubility of the enzyme systems involved in this part of the biosynthetic chain. This problem is felt strongly in other areas of biochemistry as well, and will probably not be resolved until more is known about the activities of membrane-bound enzymes and the structure of membranes themselves.

Beyond the synthesis of lipids lies an area of unknown mechanisms related to the structure and biosynthesis of proteins and the processes by which proteins and lipids are linked to form the lipoproteins involved in atherogenesis. Major contributions to this area are likely to come from

FIGURE 1

SERUM CHOLESTEROL LEVEL AT ENTRY AND AGE-ADJUSTED RATES* OF FIRST MAJOR CORONARY EVENT FOR WHITE MALES AGE 30-59 AT ENTRY NATIONAL COOPERATIVE POOLING PROJECT



*Rates for 10 Years of Followup Adjusted by Age to the U. S. White Male Population, 1960.

intensive studies in the chemistry of proteins, control of enzymes, membrane structure and function, genetics, and immunology. The existence of hereditable abnormalities of lipoprotein metabolism in man offers great opportunities for the study of genetically controlled mechanisms in humans.

The presence of lipids in biological membranes has been known for some time, but until recently techniques were not available to do much more than accurately determine their presence and distribution pattern. The development of X-ray crystallography, nuclear magnetic resonance, and electron microscopy, as well as the synthesis of model lipids have added immensely to the possibilities of studying membrane structure and function. Preliminary results indicate that the addition of cholesterol to phospholipid membranes alters their structure as well as their permeability. Great difficulties still exist in making model membranes in which proteins occupy a key part, and it is likely that a major step forward in the understanding of biological membranes will be linked to the synthesis, in the laboratory, of membranes that exhibit both enzymatic properties and selective permeabilities similar to those that are found in nature. The control of the process whereby lipids accumulate in the arterial wall, and whereby the structure of the wall degenerates, may become possible when the function of tissue membranes is better understood.

Recommendations

1. *Major research efforts should be directed towards development of animal models that parallel the hyperlipoproteinemic states found in man.*

2. Efforts to clarify the control of biosynthetic and catabolic reactions involved in the regulation of serum lipoprotein concentrations should be continued.

3. Broad knowledge about the interaction of lipids, proteins, and other constituents of biological membranes needs to be developed.

References

1. Anitschkow NN: A history of experimentation on arterial atherosclerosis in animals. Cowdry's Arteriosclerosis. Second edition. Edited by HT Blumenthal. Springfield, Illinois, CC Thomas, 1967, pp 21-44

2. Bottcher CJF: Chemical constituents of human atherosclerotic lesions. Proc Roy Soc Med 57:792-795, 1964

3. Zilversmit DB: Metabolism of arterial lipids. Atherosclerosis: Proceedings of the Second International Symposium. Edited by RJ Jones. New York, Springer-Verlag, 1970, pp 35-41

4. Roberts JC Jr, Straus R: (Editors) Comparative Atherosclerosis. New York, Harper and Rowe, Hoeber Med Div, 1965

5. Armstrong ML, Warner EI, Connor WE: Regression of coronary atheromatosis in rhesus monkeys. Circ Res 27:59-67, 1970

6. Albrink MJ, Man EB: Serum triglycerides in coronary artery disease. Arch Intern Med 103:4-8, 1958

7. Fredrickson DS, Levy RI, Lees RS: Fat transport in lipoproteins--an integrated approach to mechanisms and disorders. New Eng J Med 276:34-44, 94-103, 148-156, 215-225, 273-381, 1967

8. World Health Organization: Classification of hyperlipidaemias and hyperlipoproteinaemias. Bull WHO 43:891-915, 1970

9. Slack J, Nevin NC: Hyperlipidaemic xanthomatosis: I: Increased risk of death from ischaemic heart disease in first degree relatives of 53 patients with essential hyperlipidaemia and xanthomatosis; II. Mode of inheritance in 55 families with essential hyperlipidaemia and xanthomatosis. J Med Genet 5:4-28, 1968

10. Eder HA, Roheim PS, Switzer S: An apoprotein of the lipoprotein. Trans Ass Amer Physicians 77:259-267, 1964

11. Mahley RW, Hamilton RL, Lequire VA: Characterization of lipoprotein particles isolated from the Golgi apparatus of rat liver. J. Lipid Res

10:433-439, 1969

12. Shore B, Shore V: Apoproteins and substructure of human serum lipoproteins. Atherosclerosis: Proceedings of the Second International Symposium. Edited by RJ Jones. New York, Springer-Verlag, 1970, pp 144-150

13. Grundy SM, Ahrens EH Jr: Measurements of cholesterol turnover, synthesis, and absorption in man, carried out by isotope kinetic and sterol balance methods. J. Lipid Res 10:91-107, 1969

14. Keys A: Coronary heart disease in seven countries. Circulation 41: Suppl 1, 1-211, 1970

15. Kannell WB, Castelli WP, Gordon T, et al: Serum cholesterol, lipoproteins and the risk of coronary heart disease. Ann Intern Med, 74:1-12, 1971

16. Kinch SH, Doyle JT, Hilleboe HE: Risk factors in ischaemic heart disease. Amer J. Public Health 53:438-442, 1963

2. Therapeutic Modalities to Lower Serum Lipids and Lipoproteins

Current State of Knowledge

There is much evidence suggesting that elevated levels of serum lipids and lipoproteins may cause atherosclerosis. Therefore, a great deal of research has been carried out on therapeutic regimens which lower these levels by alterations of the diet, administration of drugs, and most recently by surgical procedures.

Effect of Diet on Serum Lipids and Lipoproteins. It is now well recognized that the quality of fat in the diet as well as the total quantity influences the concentration of serum lipids and lipoproteins. Groen[1] and Kinsell[2] were probably the first to draw attention to the lowering of serum cholesterol concentrations in human subjects by replacements of dietary animal fats by vegetable fats. This was demonstrated conclusively in numerous studies.[3] Not all vegetable fats are capable of lowering serum cholesterol[4] and marked differences exist between the effects of different animal fats. Several fish oils, for example, when tested in comparison to other fats, were found to have a cholesterol lowering effect. On the basis of the literature available to date one may conclude that, in isocaloric amounts, polyunsaturated fatty acids tend to lower serum cholesterol, monounsaturated fatty acids have relatively little effect, and saturated fatty acids tend to increase serum cholesterol. Within the latter group, the fatty acids with 14 (myristic) and 16 carbons (palmitic) appear to be relatively more effective in increasing serum cholesterol than the 18 carbon fatty acids (stearic).[5,6]

A number of investigators have shown that the cholesterol content of the diet also affects the levels of serum cholesterol.[7] It has been suggested that levels of serum cholesterol can best be lowered by reducing the cholesterol in the diet and increasing the proportion of polyunsaturated fat, or decreasing caloric intake. Furthermore, at higher levels of cholesterol intake, an increased proportion of polyunsaturated fatty acid is needed to reduce levels of serum cholesterol. In formula diets prepared with polyunsaturated fats the addition of cholesterol in amounts as high as 2 gm per day does not affect the level of serum cholesterol.[8]

As discussed earlier, many epidemiological studies have shown a strong correlation between dietary fat and serum cholesterol concentration. Other studies have, however, failed to show a significant correlation between diet and serum cholesterol concentration.[9,10] These latter studies were carried out on population groups in which dietary differences were relatively small and it is possible that the precision of the dietary survey methods was insufficient to demonstrate a correlation like that found with populations of widely differing food patterns.

The carbohydrate content of the diet can affect the level of serum triglycerides. It has been shown that in healthy individuals diets high in carbohydrate cause elevations in serum triglyceride levels.[11] Hyperglyceridemia induced by high carbohydrate diets has been called carbohydrate induced or endogenous hyperlipidemia. It is characterized by markedly increased levels of pre-β very low density lipoproteins. When such individuals are placed on low caloric diets to lose weight, the levels of VLDL decrease appreciably. These levels also decrease when the patients are placed on isocaloric low carbohydrate diets. It has been suggested that the nature of the carbohydrate may also affect the level of triglycerides but additional data are necessary to validate this conclusion.

Small scale clinical trials concerning the effects of dietary fat on morbidity and mortality from arteriosclerosis have been performed in the United States as well as in several other countries. Several of these studies lacked adequate dietary surveillance, randomization of subjects or control groups and some were carried out with patients who had already suffered a myocardial infarction (secondary trials). One may argue that the disease was so far advanced that it is not reasonable to expect an improvement in prognosis. Even in those dietary trials carried out with older subjects free of clinical disease, it is known that in most subjects arterial lesions have progressed to the irreversible stage. These and other difficulties of dietary trials have been considered in detail by Dayton and Pearce.[12] Their paper also summarizes the results of various other trials.[13,18] The feasibility of large-scale clinical trials has also been explored.[19]

Effect of Drugs on Serum Lipids and Lipoproteins. For the past 20 years much effort has been expended in developing drugs that are effective in lowering serum lipoprotein levels and which are sufficiently safe to be taken over long periods of time. These drugs have included estrogens and thyroxine and their analogs, nicotinic acid, and in recent years clofibrate and cholestyramine.[20] Clofibrate, the ethyl ester of chlorophenoxyisobutyric acid, has been shown to cause 15-25 percent reductions in elevated serum levels of very low density lipoproteins. On the other hand, clofibrate is only modestly effective in lowering the concentration of low density lipoproteins in patients with type II hyperlipoproteinemia. Furthermore, cholesterol balance studies have shown that administration of clofibrate in addition to inhibiting cholesterol biosynthesis also causes increased excretion of sterol in the stools. The magnitude of this effect appears to be unrelated to changes in serum lipoprotein levels. Clofibrate also affects a number of other biochemical processes and it is not known how it exerts its effect on cholesterol levels. The group of patients in whom clofibrate is the preferred treatment needs to be more precisely defined.

Cholestyramine, an anion-exchange resin, when taken orally, binds bile acids in the intestine. This leads to a reduction in serum cholesterol levels and is especially effective in patients with type II hyperlipoproteinemia.[21]

It must be emphasized that since these forms of therapy are used in asymptomatic individuals over many years, information about the possible long-term toxicity is highly essential. This is especially true in children where effects of such treatment on growth and maturation are not known.

A number of large scale clinical trials aimed at assessing the safety and efficacy of various drugs are now underway. The most extensive study in the United States is the Coronary Drug Project which is being carried out by the National Heart and Lung Institute. In this study, 8,341 men aged 30-64 with previous myocardial infarction have been enrolled.[22] They have been randomized and are being treated with estrogens, clofibrate, dextrothyroxine, nicotinic acid, and placebo. Thus far, no definitive conclusions can be reached from the study since enrollment of the study population was completed only in June 1969, and it is planned that the study will run 5 years. However, early data suggested that the administration of the higher dose of estrogen was associated with a possible increase in the incidence of nonfatal heart attacks and this regimen was, therefore, discontinued. It should be emphasized that this is a secondary prevention trial.

A primary trial of long term treatment with clofibrate, coordinated by the World Health Organization, is now underway in Edinburgh, Prague, and Budapest. It is planned to recruit 5,000 male volunteers aged 30-59 in each of these cities. Men are selected for treatment according to their cholesterol levels; only those individuals with serum cholesterol levels in the upper one-third of the population distribution receive treatment. Thus far, some data have been accumulated in Edinburgh. In the first 1 1/2 years of treatment, the mean serum cholesterol level fell 18 percent and triglycerides fell 28 percent. The patients with the highest levels of serum cholesterol showed the greatest percentage decrease after treatment.[23]

Surgical Treatment of Hyperlipoproteinemia. Studies in rabbits rendered hypercholesterolemic by diet showed that prophylactic bypass of the distal half of the small intestine resulted in a decrease of 96 percent in aortic cholesterol content, a 94 percent reduction in whole blood cholesterol, and prevention of atherosclerosis.[24] Similar results were obtained in dogs.[25]

During the past eight years one group of investigators has performed about 100 bypass procedures for hyperlipidemia in patients.[26] Patients were selected for surgery after dietary management had been carried out for at least three months. On the average serum cholesterol concentrations decreased markedly and this decrease was sustained. The procedure was performed in some patients with Type III and Type IV hyperlipoproteinemia and there was a marked reduction in serum triglyceride levels.[27,28] The surgical mortality was one percent. Patients who have been followed for long periods of time exhibit regression of xanthomas and arrest of peripheral atherosclerosis as judged by peripheral arteriograms. In some patients there is a transient period of diarrhea. However, in the hands of other surgeons with fewer cases more serious side effects occurred.[29] The ability to absorb Vitamin B_{12} is nearly lost, and this vitamin must, therefore, be supplemented parenterally. The patients did not experience significant weight loss.

The procedure appears to produce a marked reduction in the absorption of cholesterol; however, cholesterol biosynthesis increases but in most instances the increase is insufficient to compensate for the loss of cholesterol in the stool. Thus far, insufficient numbers of patients have been studied to evaluate the long-term effects of this treatment on the occurrence of manifestations of arteriosclerosis. Experience with this form of therapy awaits further verification by other investigators who can accumulate a similarly large number of cases. Surgical therapy for the hyperlipidemias should be considered an experimental procedure to be undertaken with utmost caution.

Hyperlipidemia is thus important since it is a risk factor susceptible to alteration. On the basis of population studies relating incidence of arteriosclerosis to levels of serum lipids it would seem desirable to under-take to reduce serum lipid levels in the population of the United States. However, this is a formidable venture since it would require changing the diet of the entire population. In order to demonstrate whether intervention of such heroic proportions should be advocated more decisive evidence is needed that lowering of serum lipids at any given age by whatever means will indeed reduce morbidity and mortality from atherosclerosis. Intervention trials designed to test the lipid hypothesis are currently in progress. Particular emphasis is being paid to patients at high risk. The ongoing studies include the Coronary Drug Project previously mentioned.

Another study is being undertaken by the Intramural Program of the National Heart and Lung Institute. In this study of 250 patients with type II hyperlipoproteinemia and who have abnormal exercise electrocardiograms, half will be treated with cholestyramine and diet and half will receive only dietary intervention. All of the subjects will be studied by coronary angiography repeated at 2 and 5 years. In addition, exercise testing will be performed every 6 months. The appearance of the coronary arteries on angiography will be used as one measure of the efficacy of the treatment.

A third program has recently been initiated and involves six cooperating groups, Lipid Research Clinics, which will assemble a population of patients with hyperlipoproteinemia. It is expected that this study will first obtain the following information: 1) Prevalence of the various types of hyperlipoproteinemia in individuals of all ages including infants and children; 2) relative morbidity as a function of the specific type of hyperlipoproteinemia; 3) improvements of methods of detection as well as classification of hyperlipoproteinemia; and 4) determination of normal levels of lipoprotein at different ages, especially in infants and children. Each of the six Lipid Research Clinics is expected to identify between 200 and 400 individuals with type II hyperlipoproteinemia. Approximately twice this number of patients would be needed for a study to obtain a statistically significant result in terms of reduction in morbidity and mortality.

Other sources of high risk patients for primary prevention studies will be the Special Centers of Research in Arteriosclerosis and in Hypertension as well as the proposed National Centers for Prevention of Arteriosclerosis described in Volume I of the report. Although these centers will have other major missions, advantage should be taken of the opportunity afforded by their patient populations to speed the trials outlined above. Conversely, the populations of the Lipid Research Clinics should be accessible to these various centers. This coordination will be, in large measure, a responsibility of the coordinating commission described in Volume I of the report.

Unresolved Problems

Numerous programs have been undertaken in order to develop therapeutic regimens capable of reducing elevated levels of serum lipids and lipoproteins. However, it is not known whether measures resulting in reduction of serum lipid and lipoprotein concentrations will also result in a lowering of the rate of occurrence of atherosclerotic clinical disease either in individuals with normal serum levels or in individuals with elevated levels.

Nor is it known what kinds of diets are most effective in lowering levels of serum cholesterol, i.e., diets low in cholesterol and saturated fats, diets with reduced fat content, or diets high in polyunsaturated fats. Possible toxicity of prolonged use of such diets remains to be studied, especially during fetal development and in children.

The selection of the most suitable drug for treatment of patients with various types of hyperlipoproteinemia needs further study.

It is not known to what extent the results obtained with drugs in patients with hyperlipoproteinemia can be extrapolated to individuals with lipid levels within the normal United States distribution.

Recommendations

1. A single large-scale national diet-heart trial is not recommended. After lengthy deliberations the Task Force concluded that such a study is not feasible at the present time.

A number of clinical trials on the effects of modifications of the diet have been performed. As mentioned earlier, in 1962 the National Heart Institute* sponsored a study to determine the feasibility of undertaking a large-scale prospective study of the prevention of coronary heart disease by dietary measures.

The Task Force considered whether a single large-scale trial should be undertaken at this time. It reviewed a large body of scientific evidence pertaining to past experience with dietary manipulations and incidence of coronary heart disease. It heard testimony from many of the scientists currently most active in the field and reviewed the recommendations made to the National Heart Institute in 1968 by the Diet-Heart Review Panel.[30] In addition, it held discussions with representatives from various governmental departments and from industry. The Task Force convened two panels of experts to consider technical aspects of a proposed protocol.

---

*National Heart Institute became the National Heart and Lung Institute in 1969.

The Task Force discussed at length the advisability of recommending to the National Heart and Lung Institute the support of a single large, long-term study to attempt to obtain evidence that through alteration of the fat content of the diet of the general population of the United States, there could be attained a reduction in mortality and morbidity from arteriosclerosis and its complications.

Upon review of all this evidence, the majority of the Task Force members felt it unwise to mount a single, major, national diet-heart trial in the general population of the United States at this time. This conclusion was based mainly on three convictions: that one might well fail to obtain the desired definitive scientific answer from this huge undertaking; that the managerial problems of carrying out a well-controlled study with such a large free living population (estimates ranging from 24,000 to 115,000 individuals) in a country where an average of 18 percent of the total population move annually, and for the lengthy period of time (7-10 years) required to obtain a sufficient number of clinical events in the study population would make the study difficult to complete; finally, in view of these uncertainties, the projections of manpower and dollar costs (ranging from $500 million to more than one billion dollars) for such a study are formidable.

The Task Force expressed serious reservations about several of the fundamental assumptions upon which the experimental design of the proposed trial was based. These included the assumptions relative to the specific reduction in serum lipids which could be achieved in a free living population, and the magnitude of the reduction in the number of arteriosclerotic events which would constitute the endpoints of the study. The Task Force was also concerned about the inevitable high dropout rate when individuals are required to adhere to rigorous dietary prescriptions for many years. Also, as the national diet undergoes subtle but important changes over a period of years, the control subjects might approach the experimental group in dietary habits, thus interfering with the evaluation of the basic hypothesis. In addition, the Task Force concluded that subjects adhering to a diet regimen would most likely modify other risk factors. This would negate some of the basic assumptions of the study and make it difficult to interpret the results. Finally, the Task Force was concerned over the loss of satisfactory control subjects over a period of years as other risk factors such as smoking habits and hypertension are affected by other national programs.

As discussed earlier in this report, the Task Force feels that a definitive test of the lipid hypothesis in the general population is urgently needed. However, in view of the great uncertainty as to the feasibility of completing a single, large,long-term study and obtaining a meaningful answer, and in view of the estimated costs in relation to this uncertainty, the Task Force does not recommend that such a single, major national study in the general population be supported by the National Heart and Lung Institute at this time. The Task Force does recommend that before considering such a major undertaking, the National Heart and Lung Institute continue with smaller, well-controlled studies, described elsewhere in this report, to determine whether lowering of blood lipids by diet or drugs will result in decreased incidence of clinical disease.

2. Intensive efforts should be made to identify high risk individuals with hyperlipoproteinemia. It is recommended that this population be utilized for trials on the effect of diet, with or without drugs, on serum lipoprotein concentrations. Mass trials with diet or drugs can be ideally undertaken in populations with hyperlipoproteinemia who are at high risk from vascular disease. Such studies can be conducted by the Lipid Research Clinics described earlier in the report. These trials would also yield conclusions as to the optimal means for treatment of this group of patients. Alternative protocols for treatment could also be evaluated in the Specialized Centers for Research in Arteriosclerosis.

3. Further study of surgical procedures for treatment of hyperlipidemia should be undertaken, rigorously comparing efficacy and safety with medical management.

References

1. Groen J, Tjong BK, Kamminga CE, et al: The influence of nutrition, individuality and some other factors, including various forms of stress, on the serum cholesterol; an experiment of nine months duration in 60 normal human volunteers. Voeding 13:556-587, 1952

2. Kinsell LW, Patridge J, Boling L, et al: Dietary modification of serum cholesterol and phospholipid levels. J Clin Endocr 12:909-913, 1952

3. Ahrens EH Jr, Blankenhorn DH, Tsaltas TT: Effect on human serum lipids of substituting plant for animal fat in the diet. Proc Soc Exp Biol Med 86:872-878, 1954

4. Keys A, Anderson JT, Grande F: Effect on serum cholesterol in man of mono-ene fatty acid (oleic acid) in the diet. Proc Soc Exp Biol Med 98:387-391, 1958

5. Grande F, Anderson JT, Keys A: Comparison of effects of palmitic and stearic acids in the diet on serum cholesterol in man. Amer J Clin Nutr 23:1184-1193, 1970

6. Hegsted DM, McGandy RV, Myers ML, et al: Quantitative effects of dietary fat on serum cholesterol in man. Amer J Clin Nutr 17: 281-295, 1965

7. Frantz ID Jr, Moore RB: The sterol hypothesis in atherogenesis. Amer J Med 46:684-690, 1969

8. Ahrens EH Jr, Hirsch J, Insull W Jr, et al: The influence of dietary fats on serum lipid levels in man. Lancet 1:945-953, 1957

9. Kannel WB, Gordon T: The Framingham Study: An Epidemiological Investigation of Cardiovascular Diseases, Section 24, Diet and the Regulation of Serum Cholesterol. Edited by WB Kannel, T Gordon. US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health

10. Kahn HA, Medalie JH, Neufeld HN, et al: Serum cholesterol: Its distribution and association with dietary and other variables in a survey of 10,000 men. Israel J Med Sci 5:1117-1127, 1969

11. Antonis A, Bersohn I: The influence of diet on serum-triglycerides. Lancet 1:3-9, 1961

12. Dayton S, Pearce ML: Prevention of coronary heart disease and other complications of atherosclerosis by modified diet. Amer J Med 46: 751-762, 1969

13. Turpeinen O, Miettinen M, Karvonen MJ, et al: Dietary prevention of coronary heart disease: Long-term experiment: I. Observations on male subjects. Amer J Clin Nutr 21:255-276, 1968

14. Leren P: The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction: A controlled clinical trial. Acta Med Scand, Suppl 466:7-92, 1966

15. Leren P: The Oslo diet heart study: Eleven-year report. Circulation 42:935-942, 1970

16. Medical Research Council: Controlled trial of soya-bean oil in myocardial infarction. Lancet 2:693-700, 1968

17. Rinzler SH: Primary prevention of coronary heart disease by diet. Bull NY Acad Med 44:936-949, 1968

18. Bierenbaum ML, Fleischman AI, Green DP, et al: The 5-year experience of modified fat diets on younger men with coronary heart disease. Circulation 42:943-952, 1970

19. American Heart Association: The national diet-heart study final report. Circulation 37:Suppl 1:1-428, 1968

20. Eder HA: Drugs used in the prevention and treatment of atherosclerosis. The Pharmacological Basis of Therapeutics. Fourth Edition. Edited by LS Goodman, A Gilman. New York, MacMillan, 1970, pp764-772

21. Fallon HF, Woods JW: Response of hyperlipoproteinemia to cholestyramine resin. JAMA 204:1161-1164, 1968

22. Coronary Drug Project Research Group: The coronary drug project: Initial findings leading to modification of its research protocol. JAMA 214:1303-1313, 1970

23. Oliver MF: A primary prevention trial using clofibrate to lower hyperlipidemia. Atherosclerosis: Proceedings of the Second International Symposium. Edited by MF Jones. New York, Springer-Verlag, 1970, pp.582-595

24. Buchwald H: The effect of ileal bypass on atherosclerosis and hypercholesterolemia in the rabbit. Surgery 58:22-36, 1965

25. Scott HW Jr, Stephenson SE Jr, Younger R, et al: Prevention of experimental atherosclerosis by ileal bypass: 20% cholesterol diet and I^{131} induced hypothyroidism in dogs. Ann Surg 163: 795-805, 1966

26. Moore RB, Frantz ID, Varco RL, et al: Partial ileal bypass: A clinical appraisal of the Minnesota study. Circulation 44:Suppl II:47, 1971

27. Buchwald H, Moore RB, Lee GB, et al: Five years experience with the use of partial ileal bypass in the treatment of hypercholesterolemia and atherosclerosis. Israel J Med Sci 5:760-764, 1969

28. Buchwald H: Ileal bypass in the treatment of the hyperlipidemias. J Atheroscler Res 10:1-4, 1969

29. Lees RS, Wilson DE: The treatment of hyperlipidemia. New Eng J Med 284:186-195, 1971

30. Report of the Diet-Heart Review Panel of the National Heart Institute: Mass field trials of the diet-heart question: Their significance, timeliness, feasibility and applicability. AHA Monograph No 28. New York, American Heart Association Inc, 1969, pp 51

B. HYPERTENSION

Current State of Knowledge

An adequate level of blood pressure is essential to maintain the circulation and perfuse the organs of the body. This level is a reflection of many variables such as: age, activity, exercise and the state of the vasculature. The blood pressure of an individual also fluctuates widely between sleeping and waking and with changes in the emotional state of the subject. Because of these variables one cannot give a single value for the (normal) level of blood pressure.

Life insurance data have established that for either sex and at any age mortality is directly related to the level of the blood pressure (whether measured as systolic or diastolic or both) down to and including the so-called normal levels. It is now recognized that the optimal blood pressure for an adult may even be below 120/80 and that some increases in mortality are experienced with elevations of only 10 to 20 mm. Hg.[1] Thus, what constitutes hypertension is difficult to determine and, therefore, the term has been variously defined. Some experts define it as a blood pressure more than two standard deviations above the mean for the age, and so arbitrarily limit the prevalence to 5 percent of the population. However, when an arbitrary value such as 150/90 or more is used to define hypertension, the prevalence of this condition is enormous. By this definition as many as 15 percent of men in their thirties and 20 percent of men in their fifties have hypertension. Thus, high blood pressure is a very common disease in the United States affecting more than 20 million Americans.

The blood pressure level rises with increasing age. At birth, it is approximately 80 mm. Hg. systolic and 40 mm. Hg. diastolic. The level continues to rise until the adult level of 120/80 is reached. The rise progresses with age until or about the age of 60 when it is usually 140/90. In the United States, mortality from hypertension and its complications is twice as high in Negroes as in whites. There is also a marked difference among the sexes in terms of clinical disease. Hypertension in the female prior to the age of 40 is less frequent and better tolerated than in the male of corresponding age, but after this age the amount of hypertension in the female exceeds that in the male. Other factors that enhance hypertension are obesity, diabetes and possibly a high salt intake.

The great majority of patients with hypertension (perhaps 80-90 percent) must be labelled "essential" due to lack of identification of a specific cause. It appears that many variables contribute to this condition. Genetic and environmental influences are such factors.[2] However, identifiable causes of high blood pressure have been discovered in increasing numbers in recent years. Almost any form of renal disease may be associated with an elevation of the blood pressure: glomerulonephritis, pyelonephritis, arteritis of the kidney, polycystic disease and various congenital lesions. These causes of hypertension have been known for many years. Interference with the arterial blood supply to the kidney, inside (renal artery stenosis) or outside (coarctation of the aorta) the organ, may result in hypertension. Recently, a vast body of information has been developed about the renin-angiotensin and aldosterone systems and their relation to high blood pressure. Elevation in blood pressure may be caused by increases in renin release (perhaps related to renal artery stenosis), increases in the renin substrate (as may be caused in some individuals by the administration of contraceptive steroids or by pregnancy), primary increases in aldosterone secretion from adenomas or hyperplastic adrenal glands and other adrenal pathology associated with hypersecretion of potential pressor hormones (Cushing"s syndrome or pheochromocytoma). Regrettably, curable causes of hypertension are identified in only a small fraction of patients. Even among those with renal artery stenosis or apparent adrenal tumor, treatment is not always successful.

Attempts to characterize patients with essential hypertension more precisely have especially involved the analyses of plasma renin activity and adrenal cortical secretion. A high plasma renin value has been encountered in approximately 10 percent if persons with essential hypertension, and a low value in about 30 percent of the cases. Further investigations have identified angiotensin and aldosterone values which, together with the plasma renin measurements, provide a biochemical profile which may lead to a better understanding of the mechanism and therapy of essential hypertension.[3] Individuals with an elevated blood pressure die (in order to frequency) from: coronary artery disease, cerebral vascular disease (thrombosis or hemorrhage); disease of the small vessels of the kidneys and atherosclerotic disease of other vessels. The first two are the most common and reflect the existence of hypertension as a potent risk factor for atherosclerosis of the coronary and cerebral arteries. Death from renal disease is seen chiefly in those persons having accelerated (malignant) hypertension, and occurs more frequently in Negroes than in whites.

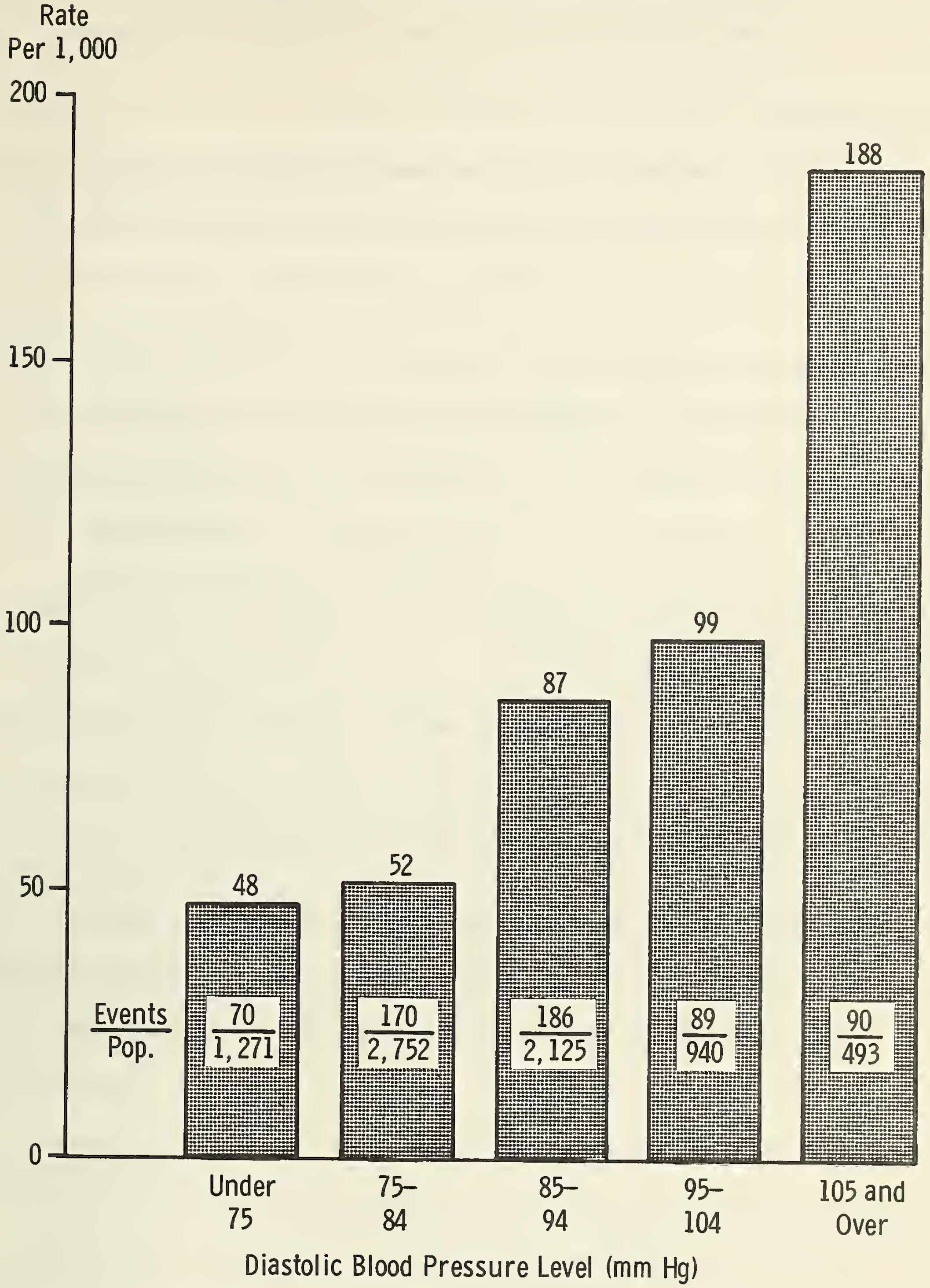
In hypertensive individuals, atherosclerosis of the coronary and cerebral arteries tends to be more severe than in normotensive persons.[4] Hypertension also promotes the formation of cerebral arterial aneurysms (Charcot-Bouchard). The risk of coronary heart disease in men age 30-59 with a diastolic blood pressure of 105 mm. Hg. or more is three times that in men with a diastolic level of 75-84 mm. Hg.(Figure 1). In the case of stroke, hypertensive men of similar age and blood pressure had nearly ten times the attack rate as men with normal levels. As the pressure increases, these risks also increase.

The recognition of the important role played by hypertension in arteriosclerosis has fortunately been paralleled by the development and availability of drugs which either lower the blood pressure to normal or lessen the hypertension significantly, in almost all cases.

A number of studies, most recently and decisively the cooperative studies in the Veterans Administration hospitals, have established the value of blood pressure control in reducing the incidence of strokes and heart failure. There is also suggestive evidence of a lessening of coronary attacks, but more prolonged observations will be required in this regard.[5] While hypotensive drugs do have certain undesirable side effects, they are nevertheless generally well tolerated over long periods and are not inordinately expensive. It is unfortunate that many cases of hypertension

FIGURE 1

DIASTOLIC BLOOD PRESSURE AT ENTRY AND AGE-ADJUSTED RATES* OF FIRST MAJOR CORONARY EVENT FOR WHITE MALES AGE 30-59 AT ENTRY NATIONAL COOPERATIVE POOLING PROJECT



*Rates for 10 Years of Followup Adjusted by Age to the U. S. White Male Population, 1960.

go unrecognized since the condition develops silently until complications occur. It has been estimated that of the more than 20 million Americans suffering from hypertension, about half are undiagnosed, and about 70 percent of those that are recognized are receiving no or inadequate treatment.

Unresolved Problems

The etiology of 80-90 percent of all hypertension remains unknown. Clearly, the identification and control or removal of a specific causative factor is crucial for the patient with established hypertension.

Detection and evaluation mechanisms are needed for the millions of persons with hypertension presently undiagnosed and untreated. Effective and economically feasible systems need to be devised. The utilization of self-administered questionnaires, allied health personnel, and automated techniques may be possible mechanisms for mounting a massive detection and diagnostic effort in hypertension.

The question whether the blood pressure remains on a set "track" from early childhood to adult life needs to be settled. Further studies are needed to determine whether this pattern can be altered by intervention.

It is currently unresolved how much effort should be expended in the attempt to define and treat the few specific recognized causes of hypertension. From the standpoint of an overall reduction of the national death rate it might be better simply to detect and treat all patients according to therapeutic regimens similar to those used by the Veterans Administration cooperative study group. There is also a controversy with respect to the level of hypertension that should be treated, and whether this decision should be made on the basis of other factors in addition to blood pressure.

Another unresolved problem is whether all persons with labile or minimal fixed hypertension should be treated. Questions which need to be answered include: should this treatment include the very young, as well as those with no evidence of complications and with no associated risk factors; and should treatment be limited only to those with complications and those with other risk factors?

The best drug or combination of drugs for mass application needs to be determined. Complications and contraindications of long-term use of these drugs need further study and requirements for adequate follow-up systems need to be developed.

Problems of long-term adherence to therapeutic regimens need definition. The causes of non-adherence need to be better understood so that appropriate measures for improving patient management can be instituted.

These are only representative of the many unresolved problems which must ultimately be faced with respect to the control of hypertension in the United States. None of these problems is simple and for none will the answer be easily obtained. But it would appear that the time has come for major and coordinated efforts aimed at answering these and related questions.

Recommendations

1. The need for earlier adequate long-term treatment of high blood pressure must be emphasized. In this regard the Task Force stresses the importance of publicizing widely to the medical profession and the public the benefits to be derived from adequate long-term treatment of mild and moderate hypertension in middle-aged males, as demonstrated by the cooperative VA high blood pressure studies. It is highly likely that similar benefits can be anticipated in the long-term treatment of hypertension in young males, and in females.

2. The Task Force endorses the plans of the National Heart and Lung Institute for a pilot program, utilizing allied health personnel under physician supervision, for detection and treatment of hypertension in adults in selected populations using test regimens.

3. A more thorough assessment of the frequency, magnitude, distribution, and natural history of elevated blood pressure in the population at all ages, including children and adolescents, should be made.

4. The role of salt intake in the genesis of hypertension, especially in children and adolescents needs to be evaluated. Infant foods prepared without added salt and clearly labeled as such should be made available to the public by manufacturers.

5. Basic research into the as yet unknown etiology of essential hypertension, including further studies of the renin-angiotensin-aldosterone system, must receive adequate support.

6. Investigations should be undertaken to evaluate further the benefits of treatment of hypertension in women, and in persons of both sexes, with labile hypertension.

7. *Additional research must be undertaken to determine the mechanism whereby hypertension is a risk factor for arteriosclerosis. It would appear that insufficient study of this problem has been carried out in the past.*

References

1. Oberman A, Harlan WR, Smith M, et al: The cardiovascular risk: Associated with different levels and type of elevated blood pressure. Minn Med 52:1283-1288, 1969

2. Paul O, Ostfeld AM: Epidemiology of hypertension. Progr Cardiovas Dis 8:106-116, 1967

3. Laragh JH: Renal and adrenal factors in hypertension: Diagnostic approaches. Bull NY Acad Med 45:859-876, 1969

4. Baker AB, Resch JA, Loewenson RB: Hypertension and cerebral atherosclerosis. Circulation 39:701-710, 1969

5. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension; II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213:1143-1152, 1970

C. SMOKING

Current State of Knowledge

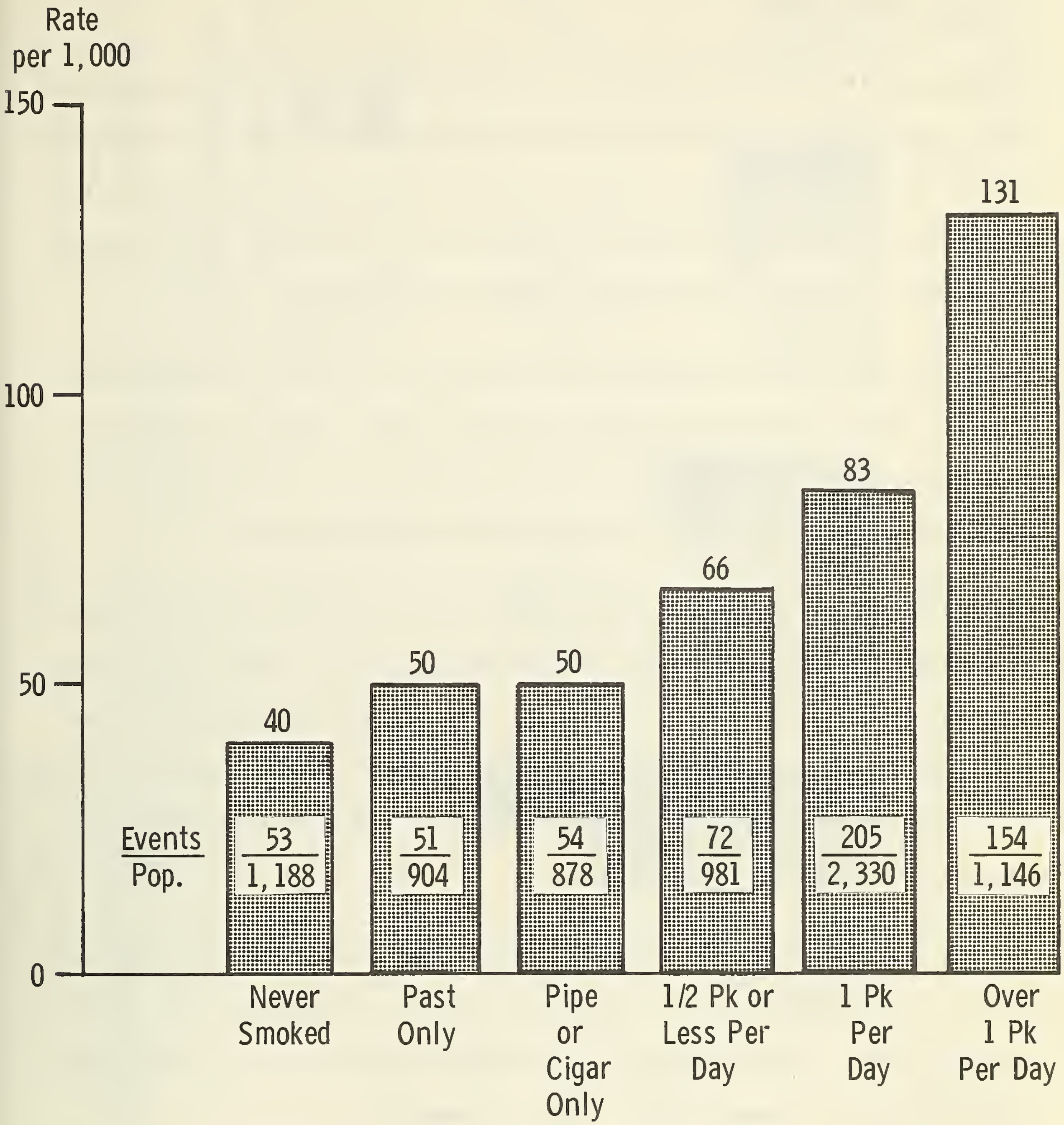
The relationship between smoking and arteriosclerosis has been reviewed in the Surgeon General's reports on Smoking and Health.[1,2] When referring to an association as significant, it is not inferred that the presence of a specific causative factor is obligatory to the development of the disease, but rather that it enhances the risk of developing the disease in a given ecologic setting. In order to justify the institution of preventive measures, it is necessary to have strong evidence in favor of a causal relationship but it is not essential to understand fully the mechanisms whereby the factor enhances risk.

Myocardial Infarction. Extensive retrospective and prospective studies have established an association between cigarette smoking and myocardial infarction.[2] The significance of this association is underscored by the observed dose response relationship and the consistency of the association from study to study (Figure 1). The lowered incidence of myocardial infarction among those who have stopped smoking suggests that the association may be causal in nature.

A study among United States veterans involved more than 11,000 deaths from coronary heart disease.[3] For all current smokers, the mortality ratio was 1.46, rising stepwise from 1.0 for non-smokers to a ratio of 2.0 for those smoking more than 39 cigarettes a day. The American Cancer Society study involved nearly 15,000 deaths from coronary heart disease among men and women 40 to 79 years of age.[4] The data shows that the greatest effect of cigarette smoking is in the younger age groups. For those smoking

FIGURE 1

CIGARETTE SMOKING STATUS AT ENTRY AND AGE-ADJUSTED RATES* OF FIRST MAJOR CORONARY EVENT FOR WHITE MALES AGE 30-59 AT ENTRY. NATIONAL COOPERATIVE POOLING PROJECT.



*Rates for 10 Years of Followup Adjusted by Age to the U. S. White Male Population, 1960.

more than 40 cigarettes a day, and who died between ages 40 to 49, the mortality ratio was 5.51; for ages 50 to 59, 2.79; 60 to 69, 1.79; and 70 to 79, 1.47 (Figure 2). A similar trend was observed in women dying of coronary heart disease.

Studies of male college students[5] and of male workers[6] also demonstrate that the coronary heart disease mortality ratio for cigarette smokers was highest among the younger age groups. This age effect on the relationship of cigarette smoking to coronary death indicates that the greatest effort should be exerted on keeping young individuals from smoking.

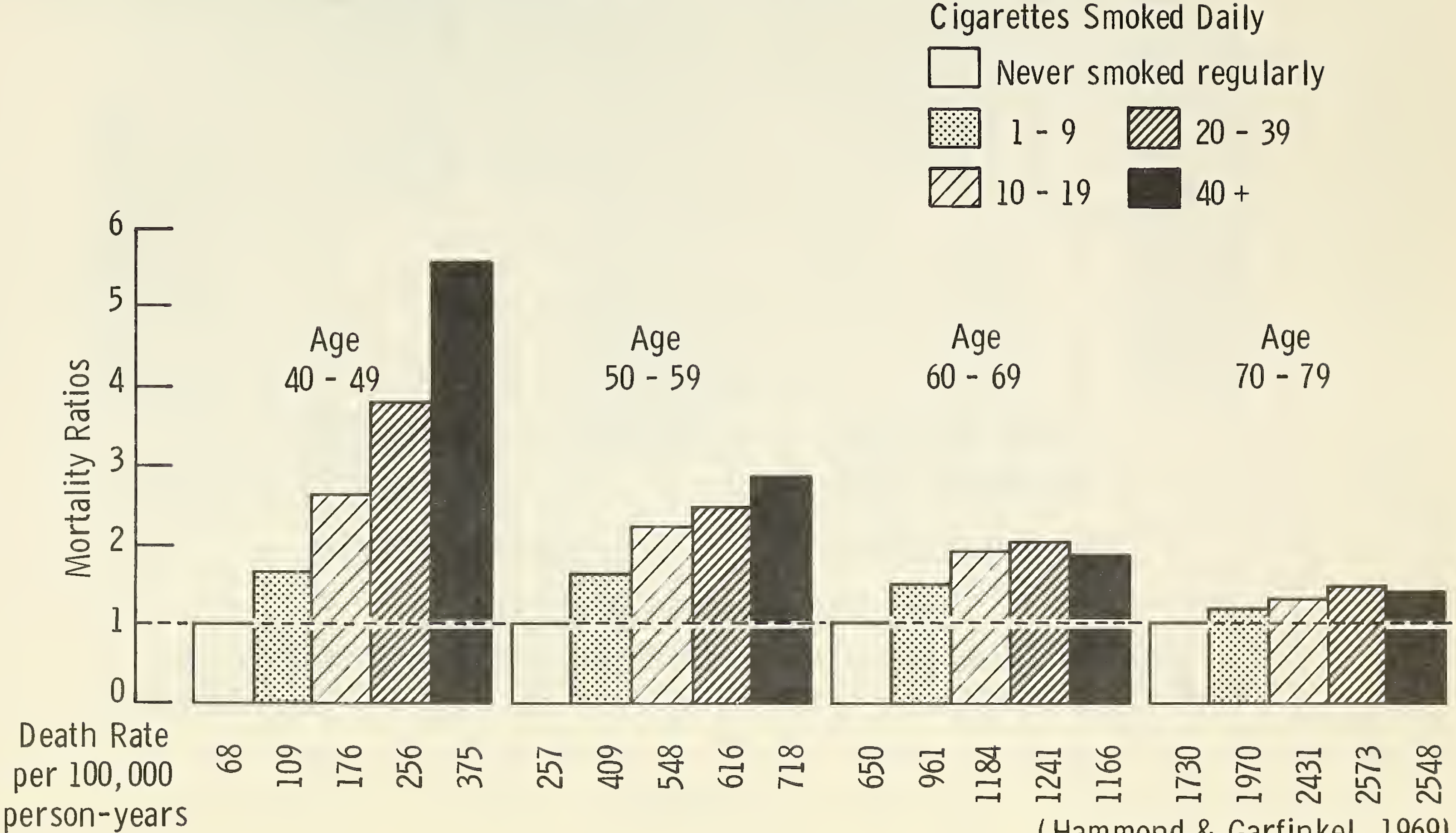
While the risk of heart attack in cigar and pipe smokers is significantly less than that of cigarette smokers, several studies report an increased risk of about 25 percent[7] and one shows an appreciable increase in risk for non-fatal myocardial infarction among cigar and pipe smokers.[8]

The relationship between cigarette smoking and myocardial infarction appears to be less in populations where atherosclerosis of the coronary arteries is less common or severe. Thus, epidemiological studies undertaken in Japan[9] and in other countries[10] where the overall incidence of myocardial infarction is relatively low, have shown no major effects of moderate smoking on the occurrence of myocardial infarction.

The combined data from the Albany and Framingham studies revealed that the effect of cigarette smoking is independent of serum cholesterol and blood pressure level, being especially high among men who have an elevated serum cholesterol level (Figure 3).[11] It thus appears that individuals with elevated levels of blood lipids are at high risk when they are also cigarette

FIGURE 2

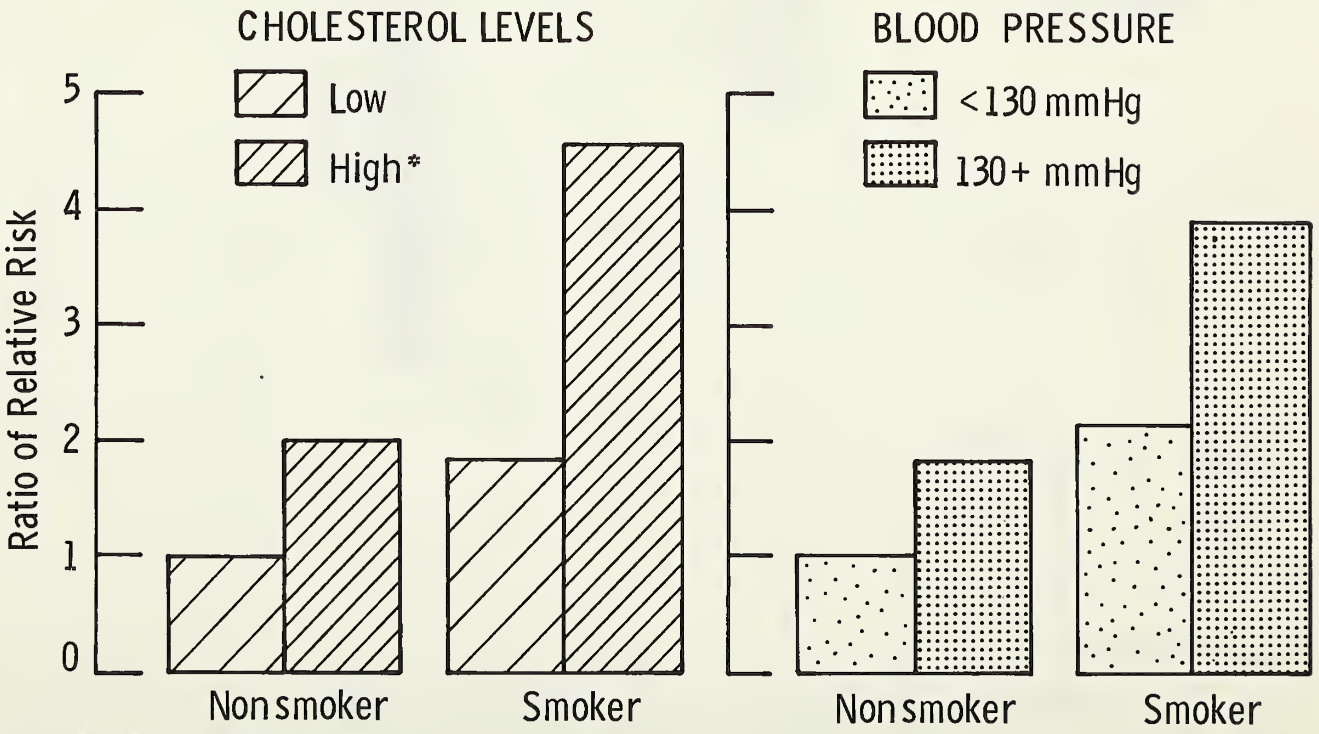
MORTALITY RATIOS AND DEATH RATES FOR CHD IN MEN BY AGE AND NUMBER OF CIGARETTES SMOKED



(Hammond & Garfinkel, 1969)

FIGURE 3

RATIO OF RELATIVE RISK FOR MYOCARDIAL INFARCTION AND CHD DEATH IN MEN AGED 30-62 BY SERUM CHOLESTEROL AND BLOOD PRESSURE LEVEL IN RELATION TO CIGARETTE SMOKING



*High ≥ 220 mg/100cc

(Doyle et al., 1964)

smokers. Subsequent 12-year follow-up from the Framingham Study shows a similar sharp risk gradient according to the amount of cigarette smoking.[12]

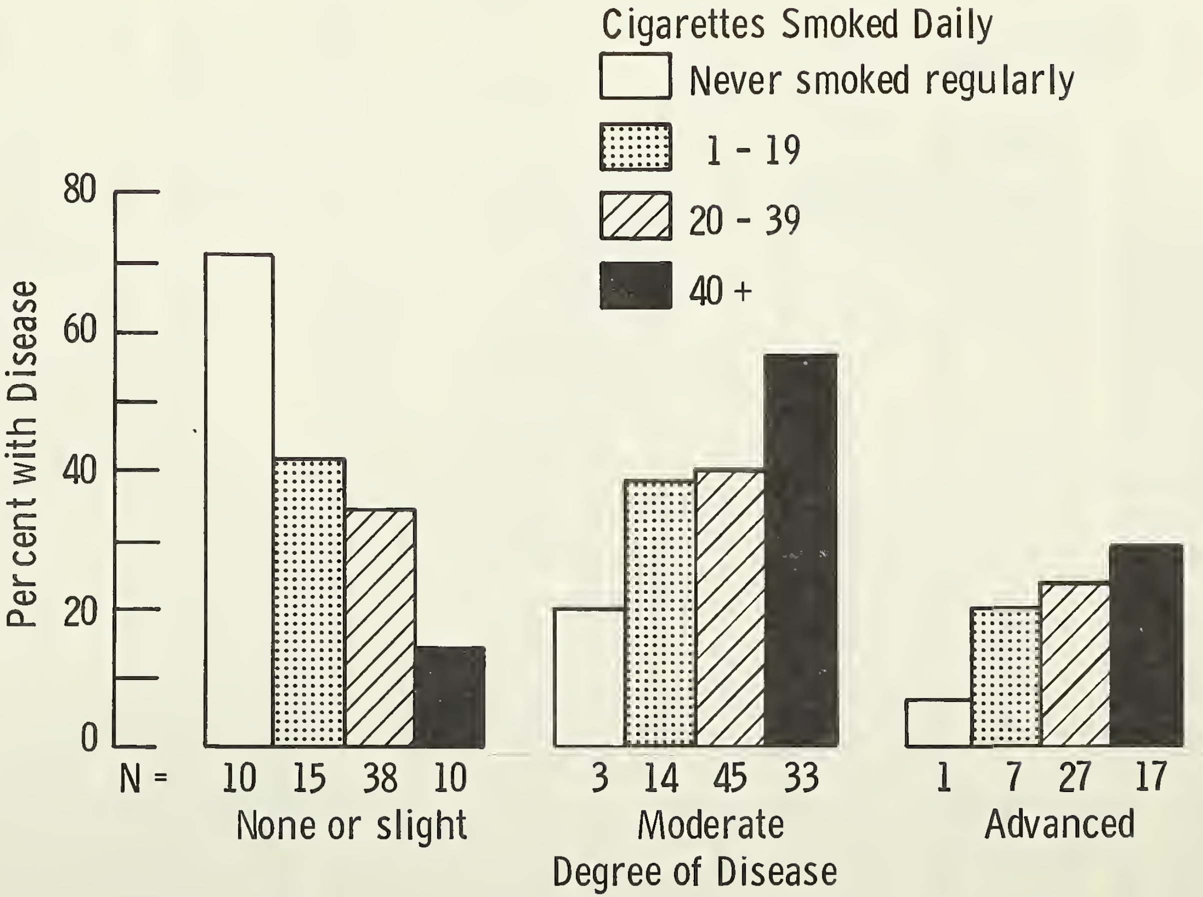
The effect of cigarette smoking on death from myocardial infarction is also indicated in other population studies. Seventh Day Adventist men (age 40) for example, have an increased life expectancy of 6.1 years over the average white male United States population of the same age[13] and develop myocardial infarction at a significantly older age than the average American male.[14] These men are non-smokers, and have lower cholesterol levels than the average American. However, their mode of life differs in a variety of ways.

In addition to enhanced risk of myocardial infarction, cigarette smokers are inclined to have more coronary atherosclerosis than non-smokers, according to several autopsy studies.[15-17] This relationship appears to be related to the number of cigarettes smoked (Figure 4).[15] However, one post mortem study of accident victims did not show this increase of coronary atherosclerosis among cigarette smokers.[18] This investigation was carried out in Chile where the population has a low level of blood lipids and a low incidence of atherosclerosis; as stated previously, cigarette smoking under these conditions may have a negligible effect on atherosclerosis and its various complications.

The effect of cigarette smoking on sudden death is demonstrated by the pooled experience of six major prospective epidemiological studies involving 154 deaths, showing that those smoking over a pack of cigarettes a day have a 3.36 times greater risk of sudden death than non-smokers (Figure 5).[7] Since sudden death constitutes some 50 percent of all deaths from acute heart attacks,

FIGURE 4

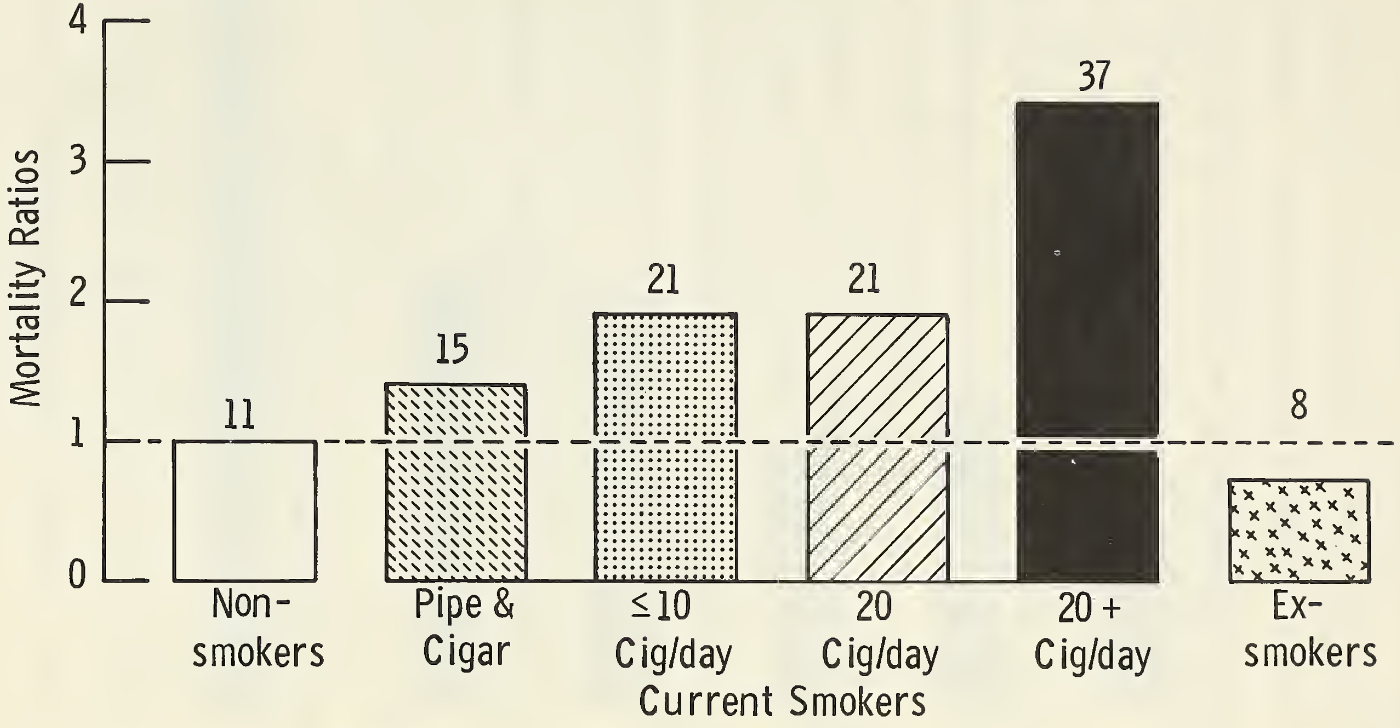
DEGREE OF CORONARY ARTERIOSCLEROSIS IN MEN AGED 45-59 BY NUMBER OF CIGARETTES SMOKED



(Auerbach et al., 1965)

FIGURE 5

MORTALITY RATIOS AND DEATH RATES* FOR SUDDEN CORONARY DEATH IN MEN AGED 30-59 BY TYPE OF SMOKING AND NUMBER OF CIGARETTES



* Age-adjusted per 1000

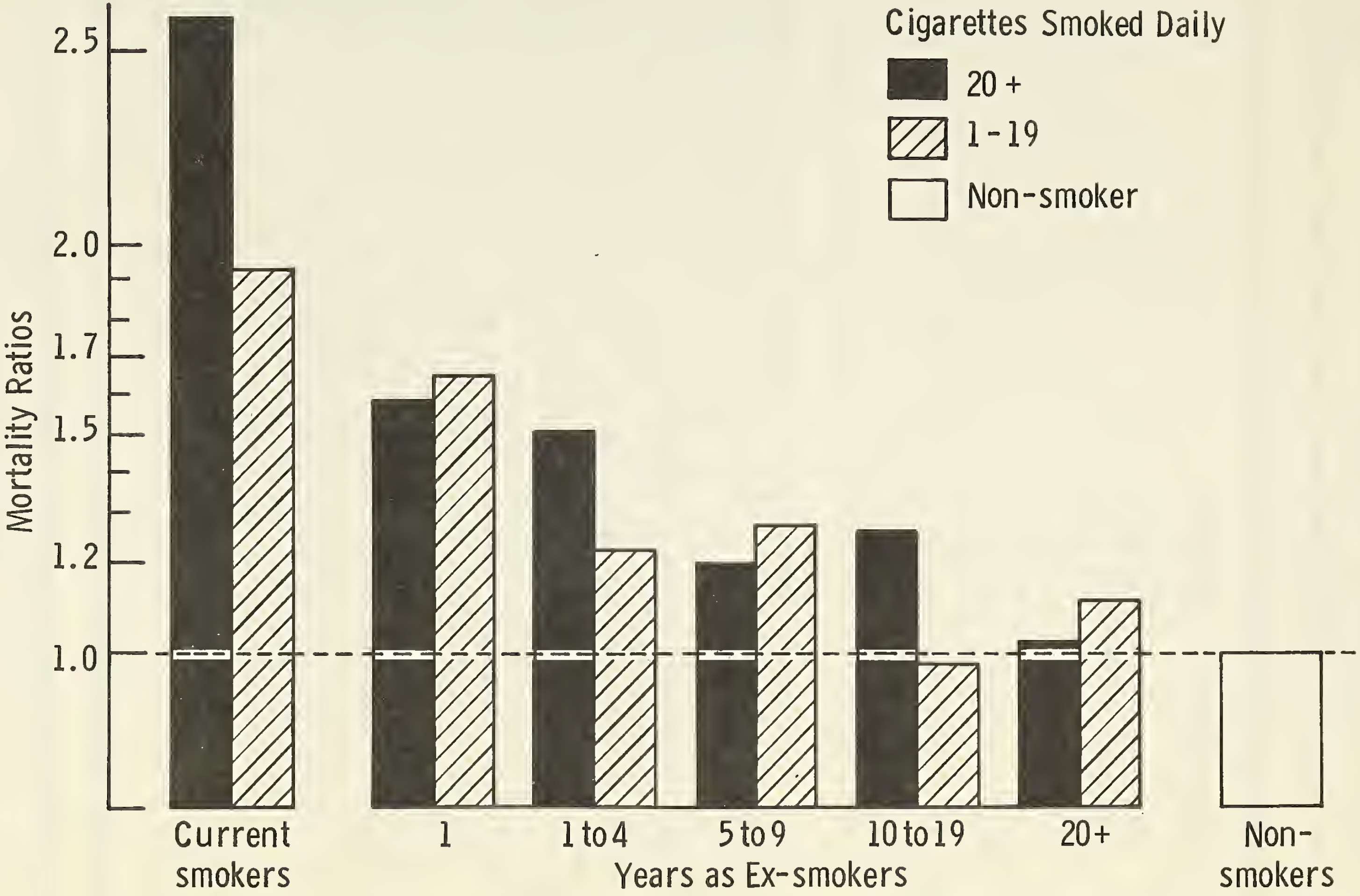
(National Cooperative Pooling Project, A.H.A., 1970) smoking is obviously a matter of great importance from the public health point of view.

Individuals who have discontinued cigarette smoking have a lower mortality from coronary heart disease, the extent of the reduction depending on a number of variables, the most important of which appears to be duration of discontinuance and amount previously smoked. Although there has been general qualitative agreement among the different studies on the lower mortality after discontinuance and on the importance of these two variables, there has been less agreement on the quantitative effects. Combined results from the Framingham and Albany studies[11,12] suggest that the coronary risk for ex-smokers reverted to the non-smoker level within a short time after discontinuance. The number on which this conclusion was based was small, however, and most other studies have failed to confirm the results. Studies based on larger groups[3,4] indicate that for moderate and heavy smokers it may take at least 10 years of discontinuance before the level of the non-smokers is reached (Figure 6) and that for those smoking one pack or more in a day it may take as much as 20 years. Those who had smoked less than 10 cigarettes a day appear to attain the level of non-smokers in a few years. However, more exact interpretation is complicated by the fact that health status may influence the decision to discontinue rather than vice versa.

The overall benefit to be gained from giving up cigarette smoking is well illustrated in the study of British physicians who have been able to stop smoking cigarettes more readily than the general population. There was a 7 percent decline in the death rate from myocardial infarction among physicians at a time when the rate in the general population increased by 35 percent.[19]

FIGURE 6

MORTALITY RATIOS FOR CHD IN MEN AGED 40-79
BY SMOKING STATUS



(Hammond & Garfinkel, 1969)

It must be taken into consideration, however, that some of this difference may be due to improvements in diagnosis of myocardial infarction in the general British population. The 6 percent decline in the overall death rate from heart disease of all types among British physicians compared with a 9 percent increase in death rate in the population as a whole may, therefore, be a more pertinent comparison.

Angina Pectoris. The combined Albany and Framingham Study, reported in 1964, which included 66 men who developed angina pectoris, did not show a relationship between cigarette smoking and angina pectoris.[11] The 1968 Framingham report revealed an increased risk for male smokers, although the difference was not significant.[12]

However, a significant association, including a clear dose response relationship, was reported in another study, based on 233 men aged 35 to 64 years in whom angina was diagnosed as a new event.[8] Smokers of 40 cigarettes or more per day, were found to have an annual age-adjusted incidence of 6.64 per 1,000, compared with a rate of 1.37 among non-smokers, while those who smoked a pack or more a day had a rate of 2.59. The criteria used for diagnosis of angina in this study varied from those used in the Framingham Study, but they were carefully defined. All these data are based on relatively few cases and additional studies will be needed before final conclusions can be drawn as to the relationship between angina pectoris and cigarette smoking.

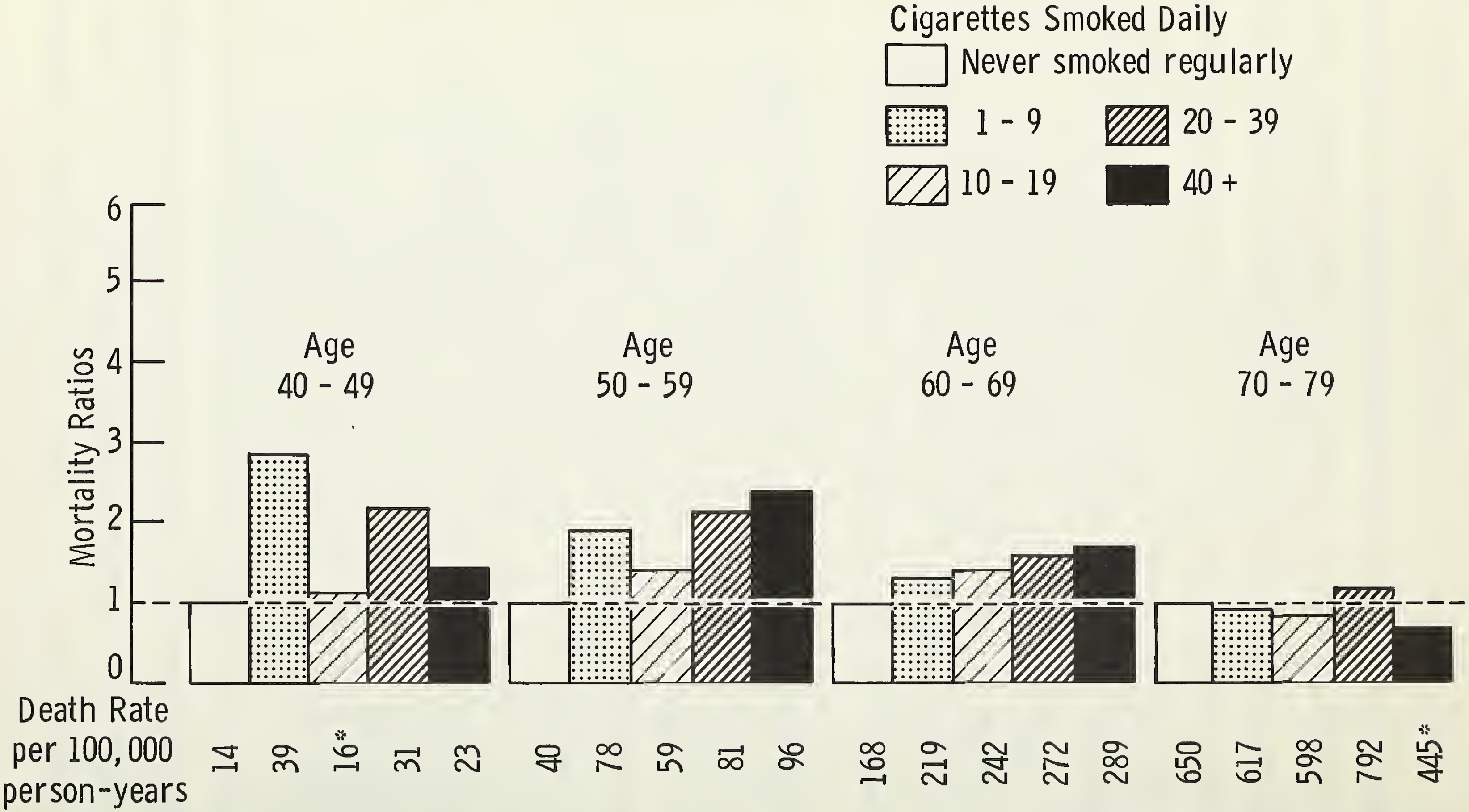
Cerebrovascular Disease. Retrospective, as well as prospective studies, show an association between cigarette smoking and stroke, although this seems to be limited to cerebral infarction.

Unlike most studies, the Framingham Study attempted to distinguish cerebral infarction from cerebral hemorrhage.[20] For men with cerebral infarction who smoked more than a pack of cigarettes per day, the study reports a mortality ratio of 1.66. The number of cases included in this study is still too small for definitive interpretation. A study of male college graduates showed a relationship of cigarette smoking to cerebral thrombosis but not to cerebral hemorrhage.[21] The study of United States veterans showed current cigarette smokers to have a mortality ratio for "cerebral vascular lesions" of 1.40.[3] Depending on age, the American Cancer Society study showed mortality ratios of 1.6-2.4 for males smoking 2 packs a day, setting the ratio at 1.0 for non-smokers. A similar trend was observed for women.[4] No clear dose-response relationship was found (Figure 7).

Peripheral Vascular Disease. The mortality from non-syphilitic aortic aneurysms, presumably due to arteriosclerosis, is significantly higher among cigarette smokers than among non-smokers. A study of approximately 360 deaths from aortic aneurysm showed a dose response relationship with individuals smoking more than 40 cigarettes per day having a mortality ratio of 8.0.[4] Similar dose response relationships were found in a study of approximately 500 veterans.[3] Since conditions like intermittent claudication are not reportable, special studies are needed to deal with this particular problem. The prospective Framingham Study showed cigarette smoking to be a significant risk factor in intermittent claudication.[22] Several retrospective epidemiological studies have also noted this condition as relatively uncommon among non-smokers.[23,24] Based on several retrospective studies in the literature, it is apparent that the occurrence of thromboangiitis obliterans or Buerger's Disease, is uncommon in individuals who have never smoked.[25]

FIGURE 7

MORTALITY RATIOS AND DEATH RATES FOR STROKE IN MEN BY AGE AND NUMBER OF CIGARETTES SMOKED



*(only 5-9 deaths)

(Hammond & Garfinkel, 1969)

Mechanisms. Although the mechanism by which cigarette smoking enhances the risk of atherosclerosis and its various clinical complications may not be fully understood, there are several components within tobacco smoke that are known to have effects on the cardiovascular system. Nicotine, for example, increases the heart rate largely through its effect on the release of catecholamines. It can transiently increase blood pressure, cardiac output, stroke volume, velocity of contraction, as well as raise myocardial oxygen consumption and induce various cardiac arrhythmias. These various responses have been investigated clinically and in animal experiments.[2,26,27] The heart with ischemic lesions is particularly susceptible to the effects of nicotine on heart rhythm and oxygen consumption.[28,29] It has also been suggested that cigarette smoking can affect blood coagulation and thrombus formation.[2] The difficulties of obtaining adequate data in acutely ill patients are apparent from recent studies.[2]

Carbon monoxide in tobacco smoke may also exert a deleterious effect through the formation of carboxyhemoglobin. It is reported that non-smokers have a carboxyhemoglobin level of 0.4 percent while the level of cigarette smokers is usually in the range of 3-10 percent.[30] In individuals with existing coronary heart disease, this loss of oxygen carrying capacity may be critical. Animals exposed to carbon monoxide exhibit a greater degree of atherosclerosis.[31,32]

Unresolved Problems

Sudden death is frequent after myocardial infarction. In appears that smoking increases the risk of sudden death, but its exact role is not known. It is not known for certain whether there is an association between angina pectoris and smoking. Appropriate criteria for angina need to be set so that the data from several studies can be compared.

Additional work is required to elucidate differences in the epidemiology of cerebral thrombosis and cerebral hemorrhage in relation to smoking. The data should clearly distinguish between these two clinical entities.

At present, it is not known whether one type of cigarette has a different effect on the rate of cardiovascular disease than another. Likewise, it is not known whether the reduction in nicotine content of cigarettes is leading to a reduction in atherosclerosis and its various clinical sequelae.

The influence of cigar and pipe smoking on atherosclerosis and its various medical complications needs further exploration. Further data would be useful to determine the role and amount of inhalation of tobacco smoke in the pathogenesis of atherosclerosis.

While available studies suggest that cessation of cigarette smoking will lead to a reduction of the incidence of myocardial infarction, the timing and degree of such a reduction is still unknown. Such information is of great practical as well as theoretical importance.

The possibility that cigarette smoking raises the levels of blood lipids deserves further study, although present evidence is that the correlation between smoking and serum lipid levels is of a low order. It appears that the effect of cigarette smoking is more pronounced in the presence of elevated blood lipids and atherosclerosis. An understanding of this interrelationship is obviously of importance.

Though there is some evidence that nicotine affects the rate of atherogenesis and its various complications, the relative interrelationship of the suggested intermediary steps requires further delineation. The possibility of threshold levels and ways in which the nicotine effect could be blocked or reduced through practical means, warrants further study. It remains to be shown to what extent, if any, carbon monoxide affects the progression of atherosclerosis or the occurrence of acute events. The possible interrelationship between cigarette smoking and thrombus formation requires further elucidation. There is a particular need to study the effect of nicotine on the normal and damaged myocardium, especially under conditions of marginal oxygen supply, in terms of hemodynamic function and electrical stability of the heart.

It is not apparent why some smokers with a given medical and biochemical background are more prone to develop atherosclerotic cardiovascular disease than others with similar characteristics. Factors that explain individual differences in susceptibility to tobacco smoking are not apparent.

Recommendations

1. To coordinate the educational aspects of risk factors including smoking and atherosclerosis, and its various clinical complications, the Task Force recommends formation of an Office of Education within the National Heart and Lung Institute. This office will initiate, stimulate, and execute educational programs in the area of smoking and other risk factors in coordination with voluntary health organizations.

2. It is recommended that the Institute actively support extensive coordinated epidemiological, clinical, and laboratory research to explore in detail the components of tobacco smoke that contribute directly or indirectly to atherosclerotic disease and to investigate their mode of action. A primary goal of such efforts should be less harmful smoking products.

3. Because of the relatively low incidence of myocardial infarction in premenopausal women, there are few epidemiological data on smoking and atherosclerosis among this group. Increased epidemiological information concerning this important segment of the population is needed. Studies on other clinical manifestations of arteriosclerosis in this population are also recommended.

4. Intensive research on psychosocial factors related to cigarette smoking should be undertaken. Studies should be conducted to determine these characteristics in smokers with a view to preventing young people from taking up the habit and motivating smokers to stop.

5. Epidemiological research should be expanded to monitor the effect of different types of cigarettes and other smoking products on atherosclerotic disease and its various clinical complications. Such an investigation has obvious practical and theoretical implications.

6. The tobacco industry should be encouraged, by legislative means if necessary, to reduce those elements in tobacco smoke that can be demonstrated to be responsible for the occurrence of the manifestations of arteriosclerosis.

7. Since the cessation of cigarette smoking seems to be a difficult task, especially for heavy smokers, it is recommended that smoking withdrawal clinics be established in institutions that provide general medical care for the public.

References

1. Report on the Advisory Committee to the Surgeon General of the Public Health Service: Smoking and Health. PHS Publication No 1103, 1964

2. A report of the Surgeon General, PHS. The Health Consequences of Smoking. PHS 1971

3. Kahn AH: The Dorn Study of Smoking and Mortality among US Veterans: Report on eight and one half years of observation. NCI Monogr No 19, pp 1-125, 1966

4. Hammond EC, Garfinkel L: Coronary heart disease, stroke and aortic aneurysm. Arch Environ Health, 19:167-182, 1969

5. Paffenbarger RS Jr, Wing AL: Chronic disease in former college students. X. The effects of single and multiple characteristics on risk of fatal coronary heart disease. Amer J Epidem 90:527-535, 1969

6. Weir JM, Dunn JE Jr: Smoking and Mortality: A Prospective Study. Cancer 25:105-112, 1970

7. Inter-Society Commission for Heart Disease Resources: Atherosclerosis Study Group and Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42:A55-A95, 1970

8. Shapiro S, Weinblatt E, Frank CW, et al: Incidence of Coronary Heart Disease in a Population Insured for Medical Care (HIP). Myocardial infarction, angina pectoris and possible myocardial infarction. Amer J Publ Health 59(6):1-101, Suppl to June 1969

9. Hirayama T: Smoking in Relation to the Death Rates of 265,118 Men and Women in Japan. National Cancer Center, Research Institute, Tokyo, September 1967, pp 1-14

10. Bronte-Stewart B, Keys A. Brock JF: Serum-Cholesterol, Diet, and Coronary-Heart Disease. Lancet 2:1103-1107, 1955

11. Doyle JT, Dawber TR, Kannel WB, et al: The relationship of cigarette smoking to coronary heart disease. The Second Report of the Combined Experience of the Albany, New York and Framingham Mass Studies. JAMA 190:108 - 112, 1964

12. Kannel WB, Castelli WP, McNamara PM: Cigarette Smoking and Risk of Coronary Heart Disease; Epidemiological Clues to Pathogenesis. Framingham Study. NCI Monogr No 28; 9-20, 1968

13. Lemon FR, Kuzma YW: A biologic cost of smoking. Arch Envir Health 18:950-955, 1969

14. Wynder EL, Lemon FR, Bross IJ: Cancer and coronary artery disease among Seventh Day Adventists. Cancer 12(5):1016-1028, 1959

15. Auerback O, Hammond EC, Garfinkel L: Smoking in relation to atherosclerosis of the coronary arteries. New Eng J of Med 273:775-779, 1965

16. Avtandilov GG, Kolenova VI, Ponomarenko OV: Kureniye tabaka i stepen' aterosklerоticheskogo porazheniya koronarnykh arteriy seveltsa i aorty. (Tobacco Smoking and the Degree of Atherosclerotic Lesions of Coronary Arteries and Aorta) Kardiologiya 5:30-34, 1965

17. Strong JP, Richards ML, McGill HC Jr, et al: On the associations of cigarette smoking with coronary and aortic atherosclerosis. J Atheroscler Res 10:303-317, 1969

18. Viel B, Donoso S, Salcedo D: Coronary atherosclerosis in persons dying violently. Arch Intern Med 122:97-103, 1968

19. A report of the Royal College of Physicians, London. Smoking and Health Now. Pitman Medical and Scientific Publishing Co Ltd 1971

20. Kannel WB, Dawber TR, McNamara PM: Vascular Disease of the Brain-Epidemiologic Aspects: The Framingham Study. Amer J of Public Health, 55:1355-1366, 1965

21. Paffenbarger RS Jr, Williams JL: Chronic Disease in Former College Students. V. Early Precursors of Fatal Stroke. Amer J Public Health 57:1290-1922, 1967

22. Kannel WB, Dawber TR, Skinner JJ Jr, et al: Epidemiological aspects of intermittent claudication: The Framingham Study. Circulation 31, 32 (Suppl II):121-122, 1967

23. Juergens JL, Barker NW, Hines EA Jr: Arteriosclerosis obliterans: Review of 520 cases with special reference to pathogenic and prognostic Factors. Circulation 21:188-195, 1960

24. Widmer LK, Hartmann G, Duchosal F, et al: Risk factors in arterial occlusions of the limbs. German Med Monthly 14:476-479, 1969

25. Razdan AN, Singh RP, Srivastana VK: Thromboangitis obliterans. A clinical study of 125 cases. Int Surg Bull 47:122-125, 1967

26. Irving DW, Yamamoto T: Cigarette smoking and cardiac output. Brit Heart J 25:126-132, 1963

27. Westfall TC, Watts DT: Effect of cigarette smoke on epinephrine secretion in the dog. Proc Soc Exp Biol Med 112:843-847, 1963

28. Balars T, Ontake S, Cummings JR, et al: Ventricular extrasystoles induced by epinephrine, nicotine, ethanol, and vasopressin in dogs with myocardial lesions. Toxic Appl Pharmacol 15:189-205, 1969

29. Bellett S, Kershbaum A, Meade RH Jr, et al: The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligations. Amer J Med Sci 201:40-51, 1961

30. Chevalier RB, Krumholz RA, Ross JC: Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. JAMA 198:1061-1064, 1966

31. Astrup P: Effects of hypoxia and carbon monoxide exposures on experimental atherosclerosis. Ann Intern Med 71:426-427, 1969

32. Webster WS, Clarkson TB, Lofland HB: Carbon monoxide - aggravated atherosclerosis in the squirrel monkey. Exp Molec Path 13:36-50, 1970

D. DIABETES MELLITUS

Current State of Knowledge

It has long been recognized that patients with diabetes have a high incidence of atherosclerosis. In one large series, vascular disease was the cause of death in three-fourths of patients with diabetes both male and female.[1] In diabetic males, aged 15 to 44, the mortality from coronary heart disease is 4.6 times higher than in non-diabetic males, and in female diabetics the death rate is 6.4 times that found in non-diabetic females.[2] Atherosclerosis is thus not only increased but it occurs at an earlier age, and the protection against coronary heart disease enjoyed by younger women is obliterated by the presence of diabetes. The incidence of peripheral vascular disease in diabetics is even greater than that of coronary heart disease.

In patients with coronary heart disease the incidence of abnormal glucose tolerance tests is almost double that expected in the population as a whole: 37.5 percent of the men and 42.1 percent of the women had abnormal glucose tolerances.[3] Elevated blood glucose has also been shown to be a risk factor in the Framingham Study, especially in respect to peripheral vascular disease.[4]

It is tempting to relate the occurrence of vascular disease in patients with diabetes or elevated levels of blood glucose to hyperlipidemia. The data from the Tecumseh Study do show a correlation between hyperglycemia and hyperglyceridemia.[5] However, in some studies normal serum lipid levels have been found in diabetics although others have reported elevated levels.[6,7,8] It is noteworthy that in Israel, individuals from North Africa and the Middle East with diabetes have a low incidence of coronary heart disease.

In Japan, the incidence of atherosclerosis, even peripheral vascular disease, in diabetics is negligible.[9] It may be that the presence of diabetes so potentiates risk factors such as hyperlipidemia that the effects of the differences in serum lipid levels between Western and Japanese populations are sufficient to account for the high incidence of atherosclerosis in diabetics in the Western world.

Certain patients with hypertriglyceridemia do have hyperglycemia. It has not as yet been determined whether such patients have genetic diabetes mellitus or whether the hyperglycemia is secondary to the hyperlipoproteinemia. Obesity is common in this group of patients and it has been suggested that the hyperlipidemia may be the result of the increased levels of plasma insulin that have also been found in these individuals.

The reason for the increased incidence of atherosclerosis in diabetics is not known. Although at times it may be related to the presence of hyperlipidemia, it occurs so frequently in the absence of high levels of serum lipids that the effect of local factors, such as increased amounts of mucopolysaccharides in the arterial wall, require further study.

Unresolved Problems

The reason why patients with diabetes mellitus have such a high incidence of atherosclerosis is not known. While patients with keto-acidosis and a small group with marked hyperglyceridemia do have very high serum levels, the levels of serum lipids and lipoproteins in the remainder of the diabetic population have not been well defined.

It is not known whether treatment directed toward lowering levels of serum lipids affects the incidence of atherosclerosis in diabetics or whether treatment of diabetes affects levels of serum lipids except in patients who are severely undertreated.

The results of the study by the University Group Diabetes Program[10] suggest that administration of tolbutamide and also phenformin results in increased mortality from cardiovascular disease. The reason is unknown and requires study. Because of this finding, the use of diet in the management of the non-insulin requiring, maturity onset diabetics, has assumed increased importance. Further study of diabetic diets in terms of their effects on serum lipids is necessary.

Recommendations

1. In facilities such as the Lipid Screening Clinics and Arteriosclerosis Research Centers, serum lipid and lipoprotein levels should be determined in a representative population of patients with pre-diabetes, chemical diabetes, and overt diabetes. Also, it should be determined whether treatment of diabetes affects levels of serum lipids and lipoproteins.

2. The most effective methods for lowering levels of serum lipids and lipoproteins in these diabetic individuals should be determined.

3. The effect of such regimens on the incidence of peripheral vascular disease, coronary heart disease, and microangiopathy needs to be evaluated.

4. Research directed toward determining how diabetes accelerates the development of arteriosclerosis should be undertaken. This would include studies of the effects of diabetes on the metabolism of the arterial wall,

studies of the role of diabetes on lipoprotein synthesis and catabolism as well as on lipid metabolism, evaluation of the role of oral hypoglycemic agents and insulin on lipid metabolism and on the metabolism of the arterial wall, and evaluation of the relationship between familial hyperglyceridemia and genetic diabetes mellitus.

References

1. Marks HH: Longevity and mortality of diabetes. Amer J Public Health 55:416-523, 1965

2. Epstein FH: Epstein FH: Hyperglycemia: A risk factor in coronary heart disease. Circulation 36:609-619, 1967

3. Ostrander LD,Jr, Francis T Jr, Hayner NS, et al: The relationship of cardiovascular disease to hyperglycemia. Ann Intern Med 62:1188-1198 1965

4. Gordon T, Sorlie P, Kannel WB: Coronary heart disease, atherothrombotic brain infarction, intermittent claudication--A multivariate analysis of some factors related to their incidence: Framingham Study, 16-year followup. Section 27. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Edited by WB Kannel, T Gordon. Washington DC, Government Printing Office, 1971

5. Ostrander LD Jr, Neff BJ, Block WS, et al: Hyperglycemia and hypertriglyceridemia among persons with coronary heart disease. Ann Intern Med 67:34-41, 1967

6. Sterky G, Larsson Y, Persson B: Blood lipids in diabetic and non-diabetic school children. Acta Paediat 52:11-21, 1963

7. Wolff OH, Salt HB: Serum-lipids and blood-sugar levels in childhood diabetes. Lancet 274:707-710, 1958

8. New MI, Roberts TN, Bierman EL, et al: The significance of blood lipid alterations in diabetes mellitus. Diabetes 12:208-212, 1963

9. Rudnick PA, Anderson PS: Diabetes mellitus in Hiroshima, Japan: A detection program and clinical survey. Diabetes 11:533-543, 1962

10. The University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 19:Suppl 2:747-830, 1970

E. OBESITY

Current State of Knowledge

Overweight has been directly or indirectly implicated in several aspects of cardiovascular disease.[1,2] These include evidence from insurance companies showing an increased death rate from cardiovascular and renal diseases in persons who are overweight; an increased prevalence of hypertension; an association with faulty ventilation of the lungs leading to a reduced oxygen tension in the blood, and the production of a type of chronic right heart disease apparently seen only in obese persons; and an association with diabetes which in turn is frequently accompanied by atherosclerosis early in life. Investigations have pointed to the differing importance of body weight *per se* and body fatness. The latter has been found to have a more significant association with coronary heart disease than weight standards, "ideal" weights, and weight-height relationships in that none of these may be properly applicable to populations with the range of varied body builds customarily encountered.

The three factors - obesity, hypertension, and diabetes - are interrelated, and each, in turn, is related to atherosclerosis. Further, certain patterns of hyperlipidemia associated with premature atherosclerosis are more common in those who are overweight. There is disagreement as to the extent of coronary disease in obese individuals without either hypertension or diabetes; most studies have shown a modest excess of coronary disease in those who are overweight.[3] Overweight is not just important in later life for it has been shown that the college student who is excessively heavy has an enhanced mortality rate from coronary heart disease later in life.[4] It is this kind of evidence and the frequency of hypertension, diabetes, and certain hyperlipidemic states in coronary heart disease and strokes, and their association with obesity, which point to obesity as an important risk factor. Further, obesity is unhappily a common health problem (one-third of a group of 6,640 middle-aged men from five different regions in the United States were more than 20 percent above ideal weight).

Unresolved Problems

Recent studies of obese individuals have revealed abnormalities in a number of metabolic parameters such as glucose tolerance and plasma insulin levels.[5] It is not evident whether these changes are the result of obesity or the cause of it. Studies of the metabolism of adipose tissue in these subjects need to be extended so that the underlying mechanisms whereby obesity affects atherosclerosis can be understood.

There are considerable data showing that the levels of serum lipids are related in part to caloric intake. Patients gaining weight have increases in their levels of serum cholesterol and triglyceride. Levels of serum triglycerides in patients with hyperglyceridemia are strikingly reduced by caloric restriction.[6] The turnover of cholesterol is altered in obese individuals. The details of these relationships require additional study.

One particular unresolved problem involves the maintenance of ideal weight in the young. This has long-term implications for atherosclerosis. The medical profession and society have not faced up to the early indentification of the obese child. They have also not been able to provide an adequate answer to the management of this problem once it has been recognized. It is believed to be important to try to prevent obesity in the middle-aged and elderly by proper habits of eating and weight consciousness in childhood and youth.

Recommendations

1. The Task Force recommends that there be support for basic research into the mechanisms through which obesity is related to the development of atherosclerosis.

2. The Task Force recommends that there be emphasis now, under the leadership of the Federal Government and in cooperation with all possible voluntary health groups, on the desirability of maintenance of ideal weight for all age groups. Well baby clinics, nursery schools, kindergarten classes, as well as Parent-Teacher Association groups, need to direct far more attention to the problem. Primary and secondary schools should be encouraged to achieve the same goal. Specific programs, based upon recommendations from parents, teachers, nutritionists, psychologists, and physicians, especially pediatricians, should be formulated and widely disseminated. Local implementation in cooperation with health and school groups would be a prerequisite to success.

References

1. Seltzer CC: Overweight and obesity: The associated cardiovascular risk. Minn Med 52:1265-1270, 1969

2. Society of Actuaries: Build and Blood Pressure Study, Volume I, 1959. Chicago, Society of Actuaries, 1960, p 268

3. Kannel WB, LeBauer EJ, Dawber TR, et al: Relation of body weight to development of coronary heart disease: The Framingham Study. Circulation 35:734-744, 1967

4. Paffenbarger RF Jr, Wing AL: Chronic disease in former college students: X. The effects of single and multiple characteristics on risk of fatal coronary heart disease. Amer J Epidem 90:527-535, 1969

5. Sims EAH, Horton ES, Salans LB: Inducible metabolic abnormalities during development of obesity. Ann Rev Med 22:235-249, 1971

6. Bierman EL, Porte D Jr, Bagdade JD: Hypertriglyceridemia and glucose intolerance in man. Hormone and Metabolic Research: Adipose Tissue, Regulation and Metabolic Functions, Supplement 2. Edited by R Levine, EF Pfeiffer. New York, Academic Press, 1970, p 209-212

F. PHYSICAL INACTIVITY

Current State of Knowledge

The scientific evidence regarding the relationship between physical inactivity and the risk of coronary heart disease is far from conclusive. Nevertheless, a great many physicians and some health organizations are actively promoting physical exercise as a preventive or therapeutic measure for coronary heart disease. It has been estimated recently that as many as 8 million adult Americans are actively engaged in regular physical exercise towards this end.

The idea that regular physical exercise decreases the danger of death or disability from coronary atherosclerotic disease is based on a number of assumptions, some proven and some of questionable validity. These include:

1) Exercise training may increase the size of the coronary arterial bed and the extent and functional capacity of the collateral circulation.

2) Habitual exercise makes the heart, the peripheral muscles and the peripheral circulation operate more efficiently.

3) Habitual physical activity may decrease the tendency for coronary atherosclerosis by modification of the known risk factors. For example, it may help to maintain ideal body weight, lessen psychic stresses, and make an individual more health and diet conscious.

4) Regular exercise may lessen the probability of coronary thrombosis by modifying the clotting mechanisms and by favorably affecting the sympathetic neuro-humoral balance.

5) Exercise may decrease the tendency towards the fatal consequences of

myocardial infarction by increasing collateral circulation, by decreasing myocardial catecholamine concentration, by increasing left ventricular mass and decreasing the likelihood of arrhythmias.

These hypotheses were developed largely from uncontrolled clinical observations by physicians over the years beginning with Heberden in 1772.[1] They have been supported recently by a number of epidemiological and hemodynamic studies although not all these investigations are in accord. A number of excellent reviews regarding this subject have been published.[2-8]

Epidemiological evidence. Much of the impetus to consider physical inactivity as a risk factor for coronary artery disease has arisen from epidemiological investigations. The following hypothesis by Morris and colleagues in a study of conductors and drivers, summarizes the proposed relationship.[9]

> "Men in physically active jobs have a lower incidence of coronary heart disease in middle age than have men in physically inactive jobs. More important, the disease is not so severe in physically active workers, tending to present first in them as angina pectoris and other relatively benign forms and to have a smaller early case fatality and a lower early mortality."

A multitude of epidemiological studies have been published, some in confirmation of this hypothesis[9-20] and others failing to provide support.[21-31]

The discrepancies between these investigations are striking, pointing out the difficulties in arriving at answers in a disease of multiple etiology such as arteriosclerosis. The difficulties are compounded if the risk factor in question, e.g. physical inactivity, is difficult to assay with precision. Judging physical activity by occupation alone, especially by last occupation, is inaccurate. People may intentionally select jobs on the basis of their health, transfer and leave jobs, and may have off-the-job activities that directly influence their level of physical fitness.

Another factor making it difficult to evaluate the possible effect of exercise is the fact that regular exercise may influence other risk factors such as serum lipid concentrations, smoking habits, obesity, and emotional stress. There is a possibility that the beneficial effects of exercise are mediated at least in part by an effect on some of these independent risk factors. In some of the studies cited above, the level of physical activity was inferred from socioeconomic stratification on the assumption that the lower, laboring classes are more physically active than are the clerical and managerial classes It is to be recognized that the question of physical activity was not directly explored in all of these studies.

In the Framingham Study it was found that the risk of death in least active males was three times that of the most active males.[15] Using three objective measurements taken as sedentary traits, (fast heart rate, obesity, and diminished vital capacity) it was determined that the death rate of subjects having all three traits was five times that of subjects having none. In contrast to this, is the prospective study by Keys et al. involving cohorts in seven countries.[27] After 120,000 man-years of observation, the difference in coronary artery disease risk between the sedentary and active groups is not evident. This suggests that if physical inactivity is indeed a risk factor, it is of much smaller magnitude than hypertension, cigarette smoking, and elevated serum cholesterol.

Another provocative report is that by Frank et al.[32] These investigators found that physically active individuals have milder infarctions and lower initial mortality than the sedentary. In this study, data as to prior physical activity was obtained retrospectively from the patients, and in the case of those who died, from their next of kin. A later published four-year follow-up of the survivors showed no difference between the active and sedentary groups.[33]

Data from Postmortem Studies. There have been three extensive postmortem studies relating level of physical activity prior to death to the degree of arteriosclerosis of the coronary arteries.[34-36] These studies suffer from the same inaccuracies in measuring the habitual level of physical activity as do the epidemiological studies. They agree on one fundamental point, that there is no major difference in the degree of coronary arteriosclerosis in sedentary as compared to physically active individuals. However, one of these studies[36] shows a decreased amount of myocardial fibrosis in the more active group, while other studies[35,37] suggest slightly less coronary artery narrowing in the more active group.

Effect of Exercise on the Coronary Arteries. One of the most frequently cited benefits of regular exercise is the possibility of an increase in the functional capacity of the collateral coronary arterial circulation. However, there is little factual information relative to this important question even in the experimental animal. In one study in dogs, moderate and severe coronary arterial narrowing resulted in extensive development of the collateral circulation in proportion to the degree of arterial stenosis.[38] Exercise, superimposed on the experimental stenosis, resulted in even greater increases in the extent of the collateral back flow. Experimental mild narrowing of the coronary artery did not provide increased collateral back flow in these animals unless exercise was superimposed. Another study, in rats, showed that mild to moderate exercise increased the size of the coronary arterial tree relative to the mass of the heart.[39]

Currens and White reported the autopsy findings of Clarence DeMar, a famous long distance runner.[40] His coronary arteries were much larger than normal (two to three times) with some atherosclerotic involvement. Studies by Rose[37] have suggested that the caliber of the coronary arteries increases with the level of occupational activity. These reports plus coronary angiographic studies of persons with large hearts due to hypertrophic subaortic stenosis and valvular aortic stenosis demonstrating unusually large coronary arteries, have led to the conclusion that this is an effect of hypertrophy secondary to exercise. Unfortunately, there is no documented evidence of increased size of coronary arteries or increase in collateral circulation as a consistent effect of physical activity or conditioning in man.

Hemodynamic Consequences of Exercise Training. It has been established that physical conditioning brings about a marked change in the cardiovascular system and in the metabolism of the heart and peripheral muscles. It has been suggested that all of these effects are present in healthy young subjects while patients with coronary artery disease have the benefit of only the peripheral changes.[41] It is also known that older subjects respond to a lesser degree to a given amount of physical training.[42] The following are well documented hemodynamic and physiological consequences of physical conditioning:

1) Relative bradycardia, increased stroke volume, and decreased systemic arterial pressure during rest and at any level of exercise

2) Longer diastolic period at a given level of exercise

3) Increased maximal oxygen uptake and maximal cardiac output

4) Increased maximal physical work capacity, and increased work capacity at any heart rate level

5) Cardiovascular hypokinesis (exercise cardiac output is less for a given oxygen uptake)

6) Increased arterial-venous O_2 difference

7) Quicker restitution of heart rate post exercise

8) Lower concentration of lactate in arterial blood at any level of work

9) Myocardial hypertrophy

10) Improved distribution of pulmonary blood flow with respect to ventilation; increased vital capacity and maximum breathing capacity in older subjects; improvement in the ventilation - oxygen uptake relationship.

11) Psychological changes - less depression, better sleeping, improvement of self-image

12) Improvement in electrocardiographic abnormalities occurring during exercise

13) Increased tolerance to exercise for persons with established angina pectoris

Recent studies have documented these effects of training in "normal" middle aged men.[43-45] Significant improvements in pulse rate, blood pressure, maximal oxygen uptake, and work capacity have also been demonstrated in individuals with prior myocardial infarctions following a period of exercise training.[46,47] In one such study approximately 80 percent of the patients showed an improvement in their exercise electrocardiogram. The death rates in the exercise groups were less than the death rate of postinfarction groups in the community. However, these studies have not been controlled and are biased by the possible loss of those higher risk patients unable to enter or to remain in the exercise program. Nevertheless, it has been shown that under proper supervision, exercise training can be carried out with reasonable safety in selected persons with coronary heart disease and with some assurance that the characteristic hemodynamic responses of the trained state will be exhibited. Importantly, the ability of these persons to tolerate physical stress may be increased and many will be able to return to a useful life.

The Effects of Exercise on Serum Lipid Concentrations, Blood Clotting Mechanisms, and Catecholamines. Exercise may decrease pre-β-lipoproteins and lower total serum triglycerides by increasing the percentage of lean body weight. On the other hand, there is no evidence that reasonable levels of exercise will significantly lower serum cholesterol on a normal diet.[48-50]

Blood coagulation may be affected acutely by physical exercise but neither the precise effect nor the mechanisms has been clearly described, although there are several studies to suggest that exercise may influence fibrinolytic activity.[51]

In animals, the catecholamine concentration of the heart muscle decreases in response to exercise. Raab and others have suggested a favorable influence on the neuro-humoral sympathetic system with exercise but there is little direct evidence to confirm such a relationship.[52]

Unresolved Problems

The major problem is whether exercise and its resulting enhancement of physical fitness offer significant protection against death or disability from coronary artery heart disease.

One of the important questions posed by recent research is that of the relationship between resting heart rate, the risk of death from coronary artery heart disease and habitual exercise. Berkson et al. have reported[53] that faster resting heart rate has an important association with risk from coronary artery heart disease and that this risk is independent of coexisting disease and other major risk factors. Since one of the characteristic responses to regular, vigorous exercise is a slowing of the resting heart rate, it is possible that resting heart rate is a more valid indication of the "fitness" of the circulation than are job descriptions or questionnaire analyses of leisure time activities.

It is evident that a related unresolved question of great importance is whether the physically trained state, defined in terms of maximal oxygen uptake or physical working capacity, materially affects the risk of coronary artery heart disease. This question has been approached thus far only indirectly through the various epidemiological studies cited earlier. It should be recognized that a clear association between physical fitness, so defined, and job classification, daily caloric expenditure or leisure time activity has not been demonstrated. Furthermore, brief periods of intense exercise may be more effective in producing the circulatory responses of the trained athlete than are more sustained levels of less severe exercise.

There is some evidence that vigorous exercise does affect the size of the coronary circulation in some species of experimental animals and there is suggestive evidence that this is also true in man. A major unresolved question is whether exercise materially affects the size of the coronary arteries or the collateral circulation in man. Direct evidence in man should be sought. However, in view of the difficulties in obtaining meaningful answers to this question in man, it seems logical that additional evidence be sought in other species, particularly in non-human primates.

In properly selected and supervised patients with coronary artery heart disease, exercise training will increase the capacity to do physical work without the induction of angina pectoris or the development of electrocardiographic abnormalities. There is also some evidence that such training will decrease the likelihood of death in survivors of acute myocardial infarction, but these important possibilities have not been fully examined. Clearly, the value of exercise as secondary prevention requires elucidation.

A major unresolved problem is determining the desirable characteristics of exercise training programs, i.e. severity of exercise, duration, frequency, differences between arm or leg exercises, and end points. For instance, does the development of resting and exercise bradycardia (relative to the untrained state) imply that an optimal effect on the coronary circulation has been achieved?

Finally, the mechanisms by which the various manifestations of exercise training are produced are decidedly unclear. It is not known to what extent the characteristic hemodynamic responses to exercise are mediated by direct effects on the heart and coronary circulation, and to what extent they are the result of peripheral changes. The effects and mechanism of exercise training on many electrophysiologic properties of the heart are not known, and therefore its role in preventing serious arrhythmia at times of myocardial ischemia or infarction cannot be answered with present knowledge.

The evidence at hand clearly demonstrates significant physiological and psychological effects of physical training that would intuitively appear to be beneficial to persons with or at risk of coronary heart disease. But there is no convincing data to indicate that exercise will, in fact, decrease either the rate of development of atherosclerosis or prevent its complications.

Recommendations

1. *A secondary prevention trial of exercise utilizing the study structure of the coronary drug study should receive careful consideration. At the conclusion of that study the National Heart and Lung Institute will have available approximately 70 percent of 8,000 carefully studied patients with coronary artery heart disease. A controlled study of exercise using the appropriate numbers of subjects and centers could be achieved at fractions of the usual cost.*

2. *Further studies of hemodynamic and metabolic responses of persons with overt coronary heart disease in response to physical training should be supported.*

3. Animal studies to examine the influence of exercise on the collateral vessels of the coronary circulation should be encouraged. Particular attention should be given to the development of methods of assessment of the collateral circulation that could be applied to man.

4. The influence of various types and duration of exercise on blood clotting mechanisms should be investigated.

5. The role of exercise on the complex interactions between caloric balance, obesity, emotional stress, serum lipid, and carbohydrate metabolism warrants further investigation.

6. The effects of exercise on the electrophysiological properties of the heart should be defined. Particular attention should be paid to its possible protective effect against serious ventricular arrhythmias under circumstances of myocardial ischemia.

7. At this time, the known facts do not support a major national effort aimed at increasing the level of physical activity for the purpose of preventing or modifying coronary heart disease. Therefore, any advice given to the public at this time must be tentative. Exercise can be recommended to increase stamina, promote a sense of well being, aid in muscular development, and in general, increase (in persons so disposed) the quality of life. But it should not be promoted as an established measure to prevent coronary atherosclerosis or its complications.

8. A clear statement should be issued as to the desirability of proper medical examination of middle-aged and elderly persons planning to participate in vigorous physical activity. This examination should include observation

of the individual while under the stress of muscular exercise, utilizing the electrocardiogram as well as physical examination. The statement should include advice relative to the characteristics of the training program that are necessary to insure its safety for older persons.

References

1. Heberden W: Classics of Cardiology. Edited by F Willins, A Keys. New York, Dover Publications Inc, I:222-224, 1941

2. Fox SM, Skinner JS: Physical activity and cardiovascular health. Amer J Cardiol 14:731-146, 1964

3. Haskell WL, Fox SM: Exercise and heart disease. Postgrad Med 177-184, 1968

4. Katz LN: Physical fitness and coronary heart disease. Circulation 35:405-414, 1967

5. Heyden S: Physical Activity Versus Inactivity. Atherosclerosis. Edited by FG Schettler, GS Boyd. Amsterdam, London, New York, Elsevier Publishing Company, 1969, pp 245-269

6. Keys A: Physical activity and the epidemiology of coronary heart disease. Medicine and Sport, Vol 4: Physical Activity and Aging. Baltimore, University Park Press, 1970

7. Naughton J, Bruhn J: Emotional Stress, Physical Activity, and Ischemic Heart Disease. Disease-A-Month. Year Book Medical Publs, Inc, 1970, pp 3-34

8. Enselberg CD: Physical activity and coronary heart disease. Amer Heart J 80:137-141, 1970

9. Morris JN, Heady JA, Raffle PAB, et al: Coronary heart-disease and physical activity of work. Lancet 2:1053-1057, 1953; Lancet 2:1111-1120, 1953

10. Morris JN, Kagan A, Pattison DC: Incidence and prediction of ischaemic heart-disease in London busmen. The Lancet 2 :553-559, 1966

11. Breslow L, Buell P: Mortality from coronary heart disease and physical activity of work in California. J Chronic Dis 11:421-444, 1960

12. Zukel WJ, Lewis RH, Enterline PE, et al: A short-term community study of the epidemiology of coronary heart disease: A preliminary report on the North Dakota Study. Amer J Public Health 49:1630-1639, 1959

13. Shapiro S, Weinblatt E, Frank CW, et al: The H.I.P. study of incidence and prognosis of coronary heart disease: Preliminary findings on incidence of myocardial infarction and angina. J Chronic Dis 18:527-588, 1965

14. Paffenbarger RS, Laughlin ME, Gima AS: Work activity of longshoremen as related to death from coronary heart disease and stroke. New Eng J Med 282:1109-1114, 1970

15. The Framingham Heart Studies:
    a. Heart Information Center, NIH: Habits and coronary heart disease, The Framingham Heart Study. Directed by WB Kannel. US Dept of Health, Education, and Welfare, Public Health Service, National Heart Institute: 1966. Washington DC, PHS Publication No 1515, p 12

    b. Kannel WB: Habitual level of physical activity and risk of coronary heart disease: The Framingham Study (Abstract). Canad Med Ass J 96:811-812, 1967

    c. Kannel WB, McNamara PM: Physical activity and risk of fatal coronary heart disease: The Framingham Study (P). Circulation 35 and 36, Suppl II:154-155, 1967

16. Werko L: Can we prevent heart disease? Ann Intern Med 74:278-288, 1971

17. Kasanen A, Kallio V, Forsström J: The significance of psychic and socioeconomic stress and other modes of life in the etiology of myocardial infarction. Ann Med Intern Fenn Suppl 43, 52:1-40, 1963

18. McDonough JR, Hames CG, Stulb SC, et al: Coronary heart disease among negroes and whites in Evans County, Georgia. J Chronic Dis 18:443-448, 1965

19. Kahn HA: The relationship of reported coronary heart disease mortality to physical activity of work. Amer J Public Health 53:1058-1067, 1963

20. Brunner D: The influence of physical activity on incidence and prognosis of ischemic heart disease. Prevention of Inschemic Heart Disease: Principles and Practice. Edited by W Raab. Springfield, Chas C Thomas, 1966 pp 1-8

21. Taylor HL, Blackburn H, Brozek J, et al: Railroad employees in the United States. Epidemiological Studies Related to Coronary Heart Disease, Characteristics of Men Aged 40-59 in Seven Countries. Edited by A Keys. Acta Med Scand, Suppl 460:55-115, 1966

22. Adelstein AM: Some aspects of cardiovascular mortality in South Africa. Brit J Prev Soc Med 17:29-40, 1963

23. a. Pell S, D'Alonzo CA: A three-year study of myocardial infarction in a large employed population. JAMA 175:463-470, 1961

    b. Pell S, D'Alonzo CA: Acute myocardial infarction in large industrial population. Report of 6-year study of 1356 cases. JAMA 185:117-124, 1964

    c. Pell S, D'Alonzo CA: Immediate mortality and five-year survival of unemployed men with a first myocardial infarction. New Eng J Med 270:915-922, 1964

24. Villiger U, Heyden-Stucky S: Das infarktprofil: Unterschiede zwischen Infarktpatienten und Kontrollpersonen in der Ostschweiz. Schweiz Med Wschr 96:748-758, 1966

25. Forssman O, Lindegard B: The post-coronary patient: A multidisciplinary investigation of middle-aged Swedish males. J Psychosom Res 3: 89-169, 1958

26. Chapman JM, Massey FJ: The interrelationship of serum cholesterol, hypertension, body weight and risk of coronary disease; Results of the first ten years' follow-up in the Los Angeles Heart Study. J Chronic Dis 17:933-949, 1964

27. Keys A: Coronary Heart Disease in Seven Countries. Circulation 41, Suppl 1:1-211, 1970

28. Paul O, Lepper MH, Phelan WH, et al: A longitudinal study of coronary heart disease. Circulation 28:20-31, 1963

29. Stamler J, Lindberg HA, Berkson DM, et al: Prevalence and incidence of coronary heart disease in strata of the labor force of a Chicago industrial corporation. J Chronic Dis 11:405-420, 1960

30. Shanoff HM, Little A, Murphy EA, et al: Studies of male survivors of myocardial infarction due to "essential" atherosclerosis, 1. Characteristics of the patients. Canad Med Ass J 84:519-530, 1961

31. Lilienfeld AM: Variation in mortality from heart disease: Race, sex and socio-economic status. Public Health Rep 71:545-552, 1956

32. Frank CW, Weinblatt E, Shapiro S, et al: Physical inactivity as a lethal factor in myocardial infarction among men. Circulation 34: 1022-1033, 1966

33. Weinblatt E, Shapiro S, Frank CW, et al: Prognosis of men after first myocardial infarction: Mortality and first recurrence in relation to selected parameters. Amer J Public Health 58:1329-1347, 1968

34. Spain DM, Bradess VA: Occupational physical activity and the degree of coronary atherosclerosis in "normal" men: A postmortem study. Circulation 32:239-242, 1960

35. Mitrani Y, Karplus H, Brunner D: Coronary atherosclerosis in cases of traumatic death: The influence of physical occupational activity on the development of coronary narrowing. Medicine and Sport, Vol 4, Physical Activity and Aging. Baltimore, University Park Press, 1970, pp 241-248

36. Morris JN, Crawford MD: Coronary heart disease and physical activity of work. Evidence of a national necropsy survey. Brit Med J II:1485-1496, 1958

37. Rose G, Prineas RJ, Mitchell JRA: Myocardial infarction and the intrinsic calibre of coronary arteries. Brit Heart J 29:548-552, 1967

38. Eckstein RW: Effect of exercise and coronary artery narrowing on coronary collateral circulation. Circ Res 5:230-235, 1957

39. Stevenson JAF, Feleki V, Rechnitzer P, et al: The effect of exercise on coronary tree size in the rat. Circ Res 15:265-269, 1964

40. Currens JH, White PD: Half a century of running: Clinical, physiologic and autopsy findings in the case of Clarence DeMar ("Mr Marathon") New Eng J Med 265:988-993, 1961

41. Clausen JP, Larsen OA, Trap-Jensen J: Physical training in the management of coronary artery disease. Circulation 40:143-154, 1969

42. Roskamm H, Reindell H: Optimal patterns of exercise for healthy adults. Medicine and Sport, Vol 4: Physical Activity and Aging. Baltimore, University Park Press, 1970, pp 19-27

43. Siegel W, Blomqvist G, Mitchell JH: Effects of a quantitated physical training program on middle-aged sedentary men. Circulation 41:19-29, 1970

44. Pollock ML, Miller HS Jr, Janeway R, et al: Effects of walking on body composition and cardiovascular function of middle-aged men. J Appl Physiol 30:126-130, 1971

45. Hanson JS, Tabakin BS, Levy AM, et al: Long-term physical training and cardiovascular dynamics in middle-aged men. Circulation 38:783-799, 1968

46. Hellerstein HK, Hornsten TR, Goldbarg A, et al: The influence of active conditioning upon subjects with coronary artery disease. Canad Med Ass J 96:758-760, 1967

47. Gottheiner V: Long-range strenuous sports training for cardiac reconditioning and rehabilitation. Amer J Cardiol 22:426-435, 1968

48. Holloszy JO, Skinner JS, Toro G, et al: Effects of a six-month program of endurance exercise on the serum lipids of middle-aged men. Amer J Cardiol 14:753-760, 1964

49. Kohn RM: Inability of physical exercise to alter serum-cholesterol levels (Abstract). Circulation 29 and 30; Suppl 3:18, 1964

50. Heyden VS, Bickel J, Blohmke M: Beeinflussung des Cholesterinspiegels durch körperliches Training? Med Klin 61:908-912, 1966

51. Guest MM, Celander DR: Fibrinolytic activity in exercise. Physiologist 3:69, 1960

52. Raab W: Preventive Myocardiology: Fundamentals and Targets. Springfield, Ill, Chas C Thomas, 1970, pp 227

53. Berkson DM, Stamler J, Lindberg HA, et al: Heart rate: An important risk factor for coronary mortality--ten-year experience of the Peoples Gas Co., epidemiologic study (1958-68). Atherosclerosis: Proceedings of the Second International Symposium. New York, Springer-Verlag, 1970, pp 382-389

G. GENETIC ASPECTS

Current State of Knowledge

It is generally agreed that a hereditary component is important in the etiology of arteriosclerosis, but there is little solid information available as to the exact nature of the genetic mechanisms involved.[1] In the case of coronary atherosclerosis the evidence that genetic factors contribute to its pathogenesis is based on observations derived from three sources: familial aggregation studies, twin studies, and analysis of risk factors.

Familial Aggregation Studies. The most recent and complete familial aggregation study on coronary artery disease was carried out in London.[2] All first degree relatives of 200 coronary artery disease index cases, both male and female, were studied. It was found that the young relatives (males under age 55; females under age 65) of young female index cases (under age 65) had a seven-fold increased risk of death from coronary occlusion compared to the general population. The risk of coronary death among the relatives (both young and old) of old (males age 55 and above; females age 65 and above) index myocardial infarction patients was approximately doubled. These data, together with earlier studies from this country[3,4] firmly establish the familial aggregation of coronary disease and provide the basis for our suspecting that genetic factors may be important. Since familial aggregation of a trait can be produced by environmental factors as well as genetic factors, these studies *per se* do not unequivocally prove the genetic basis of coronary artery disease.

Twin Studies. One of the best methods for quantitating the role of genetic factors in a common disease like coronary artery disease is the twin method. What the twin method does is to compare the rate of similarity or concordance of monozygotic twins (genetically identical) with that of dizygotic twins (genetically no more alike than any two sibs). If genetic factors contribute significantly to the disease in question, the concordance rate for identical twins should be higher than that for nonidentical twins. In the case of coronary artery disease, early studies from the Danish Twin registry, which contains complete medical information on all twin pairs born in Denmark in the period between 1870 and 1910, do not indicate a significantly higher concordance rate for myocardial infarction in monozygotic twins than in dizygotic twins of both sexes.[5] On the other hand a significantly higher concordance rate in monozygotic than in dizygotic pairs was demonstrated both for hypertension and stroke in this group of individuals.

Analysis of Risk Factors. An examination of the risk factors for coronary atherosclerosis (hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, hypertension, obesity, personality type, etc) indicates that each of these factors individually is the result of the interaction of many genes and many environmental factors. This suggests that in most forms of coronary atherosclerosis, like in other common familial diseases, the etiology is multifactorial with a strong polygenic component. The biochemical identification and elucidation of the regulation of the expression of each of the many genes contributing to the atherosclerotic process, although admittedly an awesome task, remains the ultimate goal in the study of the genetics of this disorder.

Of the above mentioned risk factors, a genetic influence has been best established for diabetes, hypertension, and some cases of hypercholesterolemia.

Manifestations of atherosclerosis occur with greater frequency among diabetics than non-diabetics. The severity of the atherosclerosis is greater, the mortality rate higher, and there is an increased incidence of premature myocardial infarction among diabetics. Furthermore, individuals with asymptomatic hyperglycemia exhibit an increased incidence of coronary, cerebral, and peripheral atherosclerosis when compared with those with normal carbohydrate metabolism.

Familial influence on blood pressure has been demonstrated.[4] The blood pressure of an individual is reflected in his first order relatives and this familial influence is measurable in children between 2 and 14 years of age.

The available evidence to date suggests that the familial hyperlipoproteinemias may be the most common single gene-determined causes of atherosclerosis, especially in young adults. Of the three phenotypic forms of hyperlipoproteinemia[6] that predispose to the development of coronary artery disease (type II or hyper-β-lipoproteinemia; type III or broad β disease; and type IV or endogenous hypertriglyceridemia), familial type II is the only one that has been conclusively shown to be inherited in a simple Mendelian pattern and is presently the only well-documented monogenic cause of coronary atherosclerosis.

Unresolved Problems

It is not known to what extent any genetic influence that does exist in atherosclerosis is due to differences in the metabolism of lipoproteins or carbohydrates, to structural differences in arteries, to predisposition to hypertension, or to other factors. To demonstrate that certain types of atherosclerosis are hereditary, it will be necessary to show that their occurrence conforms to some Mendelian pattern of inheritance.

Since most common diseases with a polygenic causation like atherosclerosis are genetically heterogeneous in etiology, it is not surprising to find several forms of the disorder for which a single mutant gene is largely responsible. The importance of identifying each of the forms of atherosclerosis that is determined by a single mutant gene is that the inheritance pattern in such cases is clear-cut and the predominant cause of the atherosclerosis is likely the result of a single and a specific biochemical lesion. An understanding of the pathophysiology of each of the specific biochemical derangements occurring in such monogenic forms of atherosclerosis will undoubtedly provide the putative information necessary for formulating a more rational approach to the biochemical and genetic investigations of the more complex and more common forms of atherosclerosis which are polygenically determined. Future research on the genetics of coronary atherosclerosis should be aimed at identifying and characterizing each of the monogenic forms of atherosclerosis.

Although the familial nature of the type III and type IV forms of hyperlipoproteinemia has been clearly documented and the data are partially suggestive of Mendelian inheritance, there is as yet insufficient information to define the precise mode of inheritance.

In order to investigate the genetic relationship between these hyperlipiemic states and coronary atherosclerosis, detailed family and genetic studies including spouses as well as first, second and third degree relatives are needed.

The importance of and need for good genetic studies on the hyperlipidemic disorders predisposing to coronary artery disease cannot be overemphasized. Accurate assessment of therapeutic regimens, genetic counseling of families, and determinations of predisposition to coronary artery disease must ultimately be related to specific genetic disorders.

Age and environmental factors make it extremely difficult to establish the genetic component of atherosclerosis in man whereas, in an experimental model, these factors can be controlled. Recent evidence has been presented that squirrel monkeys have a striking individuality in their response to an atherogenic diet.[7] Some monkeys fed an atherogenic diet show slight increases in serum cholesterol concentrations, while others attain exceedingly high concentrations. In further studies, age and environmental influences were minimized by using progeny born in the same breeding season, all of whom consumed a single diet under identical conditions of housing. The investigators were able to arrive at an estimate of hereditability that they believed was of the order of 90 percent in these animals. It is not known at this time whether or not hypo- and hyper-responders exist in humans.

Recommendations

1. Population genetic studies should be designed and undertaken in order to answer the following broad questions concerning the genetic aspects of hyperlipoproteinemia in relation to coronary atherosclerosis: How often is familial coronary arteriosclerosis attributable to familial hyperlipoproteinemia; what is the relative frequency of genetic hyperlipoproteinemia in an unselected population with coronary arteriosclerosis; among the genetic forms of hyperlipoproteinemia in this group, what proportion is due to a single mutant gene, what proportion to a polygenic causation, and what proportion to nongenetic factors; to what extent does monogenic hyperlipidemia correlate with monogenic arteriosclerosis; how are the single gene-determined forms of hyperlipoproteinemia in an unselected population with coronary atherosclerosis distributed between the various types of hyperlipoproteinemia; does the metabolism of lipids and lipoproteins in patients with monogenic hyperlipidemia differ from those with polygenic hyperlipidemia; and can improved methods of classification of hyperlipoproteinemia be developed from such studies?

2. For each of the hyperlipidemic states found to be inherited in a simple Mendelian pattern and correlated with the development of coronary atherosclerosis, the following studies are greatly needed: Assessment of the population frequency of the mutant gene; genetic analysis including determination of penetrance, sex ratios, biologic fitness, segregation ratios at each decade of life, and variability in expression of the mutant gene; attempts to discover genetic linkage relationships between the mutant gene and recognized protein genetic markers by carrying out formal linkage studies on well-chosen pedigrees; investigations at the cellular level to identify the primary biochemical defect; and establishment in tissue culture of hyperlipidemic cell lines in order that biochemical markers can be identified and cell genetic studies eventually carried out

on those disorders due to a single mutant gene.

3. Continued study of the genetics of hypercoagulable states including thrombus formation, platelet function, and fibrinolysis should be supported.

4. Support for investigation of the genetic aspects of atherosclerosis, utilizing sub-human primates, should receive high priority.

5. An investigative program should be initiated to determine whether or not genetic differences in response to cholesterol ingestion exist in humans.

6. The role of familial and genetic factors in the development of hypertension should be investigated and it would be important to carry out such studies in children. These investigations should evaluate familial aggregation and attempt to separate genetic from environmental factors.

References

1. Murphy EA: Some difficulties in the investigation of genetic factors in coronary artery disease. Canad Med Ass J 97:1181-1192, 1967

2. Slack J, Evans EA: The increased risk of death from ischaemic heart disease in first degree relatives of 121 men and 96 women with ischaemic heart disease. J. Med Genet 3:239-257, 1966

3. Gertler, MM, White PD: Coronary Heart Disease in Young Adults: A Multidisciplinary Study. Cambridge, Harvard University Press, pp 210, 1954

4. Thomas CS, Cohen BH: The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes. Ann Intern Med 42:90-127, 1955

5. Harvald B, Hauge M: Hereditary factors elucidated by twin studies. Genetics and the Epidemiology of Chronic Diseases. Edited by JV Neel, MW Shaw, WJ Schull, US Department of Health, Education, and Welfare, Public Health Service, Division of Chronic Diseases, 1965. Washington, DC, Government Printing Office (PHS Publication No 1163), p 61-76

6. Fredrickson DS, Lees RS: Familial hyperlipoproteinemia. The Metabolic Basis of Inherited Disease. Edited by JB Stanbury, JB Wyngaarden, DS Fredrickson, New York, McGraw-Hill, 1966, p 429-485

7. Clarkson TB, Lofland HB Jr, Bullock BC, et al: Genetic control of plasma cholesterol: Studies on squirrel monkeys. Arch Path 92:37-45, 1971

H. PSYCHOSOCIAL FACTORS

Current State of Knowledge

Although the known risk factors are of considerable importance in predicting the occurrence of manifestations of arteriosclerosis, an appreciable number of patients with arteriosclerotic disease exhibit none of these factors. Conversely, many persons found to have a given risk factor do not experience overt arteriosclerotic disease in the five or ten-year period after discovery of the risk factor.[1] These facts have encouraged a continuing search for other variables which may improve the ability of the epidemiologist and clinician to identify those persons at highest risk of developing atherosclerosis. Psychological, social, and behavioral conditions are receiving increasing attention as pointers to the kinds of people or situations in which a high prevalence of atherosclerosis and its complications may be found. Furthermore, failure of adherence to prescribed regimens is a major limiting factor in programs directed toward risk factor control and early treatment of the complications of arteriosclerosis. Determination of the psychosocial basis of such behavior is very necessary to greater success in these programs.

Psychosocial and behavioral factors may be considered to exert their impact on coronary disease risk through three major avenues: 1) through elevating other commonly accepted risk factors; 2) through an independent pathological effect mediated by neuro-physiological mechanisms as yet unspecified; and 3) through affecting the coronary patient's acceptance of medical care.

Psychosocial influence on risk factors. Several coronary risk factors are manifestly behavioral in nature and thus could most effectively be studied through the disciplines of the behavioral sciences. Cigarette smoking is a habit learned in a social context. Cigarette smoking has certain reinforcing properties which tend to increase its frequency of occurrence and its resistance to extinction. Recent field studies have shown that behavior modification techniques (based on the principles of operant conditioning) are often successful in bringing this habit to a halt.[2] Over-eating is the behavioral basis for most obesity, another coronary risk factor. Food selection patterns are associated with culture and social class. Eating behavior has deep psychological roots which have been the subject of considerable psychiatric study.[3] Regular physical exercise may be protective against atherosclerosis. This too is an overt behavior, but its psychosocial antecedents have not as yet been adequately studied. Increased knowledge regarding all three of the above problems would have great potential value for increasing the effectiveness of coronary prevention programs.

Two other major coronary risk factors are most appropriately considered physiological in nature; nevertheless, they are influenced by psychosocial variables. It is an established clinical observation that blood pressure increases under conditions of anxiety or anger. A large number of experimental studies have shown the influence of external events and internal emotions on blood pressure reaction.[4] Most of these studies have demonstrated rises in blood pressure lasting only for brief periods of time, and it has not been adequately documented whether the same kinds of circumstances can lead to prolonged elevations of pressure which would contribute to coronary disease risk. A variety of evidence now suggests that personality and emotion are among the several categories of factors that influence serum lipids.[5] The emerging generalization is that either excessive excitation or strong suppression of impulses can lead to elevated serum cholesterol. There is some suggestion that the very low density lipoproteins may be more subject to emotional influence, but studies have been too few to establish a consensus.[6] The evidence for cholesterol, however, is sufficient to warrant further intensive study.

Psychosocial factors as independent precursors of coronary disease. Certain psychological, sociological, and overt behavioral factors have been shown in repeated studies to be associated with an elevated risk of developing coronary disease independent of any association with standard biological risk factors. At this point in time, it is not known through which neurological or physiological mechanisms these psychosocial factors might operate. They appear to be involved at different times in the natural history of the development of coronary disease. In terms of this time frame, we can categorize these psychosocial variables as predispositions, precipitants, and reaction styles.

Predispositions. Epidemiologic studies have shown that persons who undergo a major change in their cultural environment have increased risk of coronary disease. These changes, termed social mobility, include moving to a new nation, from a farm to the city, changing one's career or one's social status.[7] A related group having increased coronary risk are those persons experiencing status incongruity.[8] By this is meant the situation where different social characteristics of a person simultaneously place him at different levels of the social hierarchy. Social scientists hypothesize that both social mobility and status incongruity are likely to increase feelings of personal insecurity and hence produce "stress." The association of social status, *per se* with coronary risk appears to be different in industrialized countries as compared to developing countries.

A particular pattern of overt behavior has been shown to predispose its possessors to increased risk of coronary disease. This "coronary prone behavior pattern" has been defined by Friedman and Rosenman to include extremes of competitiveness, aggressiveness, haste, impatience, and restlessness. Such persons are under the pressure of time and the challenge of responsibility to a far greater extent than average.[9] Rosenman and colleagues have undertaken prospective epidemiologic studies which have confirmed their hypothesis.[10] In addition, other researchers have corroborated these findings in cross-sectional studies.[11,12] Also, workers in several countries have used independent methods to study aspects of this coronary prone pattern, such as deep involvement in job, exaggeration of the "success ethic," inability to relax, and high levels of drive. They found these behavior traits to be more common in coronary patients than in various control groups.[13,14] Studies using self-administered, computer-scored questionnaires have now confirmed these findings.[15]

Precipitants. In this category are included those life events and feelings about them which are reported to be particularly frequent in time periods immediately before the clinical emergence of coronary disease. Some workers lump all these phenomena under the general term "stress" but others assert that scientific understanding can be increased only if precise definitions of the phenomena are retained instead of the "catch all" concept of stress. Several studies report that coronary events have often been preceded by some type of severe personal loss, such as death of a loved one, loss of a job, financial reversal, or loss of self-esteem such as occasioned by the breakup of a love relationship.[16] Other workers implicate work overload, including long hours of overtime work or increasing burdens of job responsibility, as temporal antecedents to the emergence of coronary disease.[17,18] A period of depression and fatigue--a worn-out feeling--often precedes clinical coronary disease.[19]

Life dissatisfactions are typically more frequent in coronary patients than in various control groups. Most, but not all, of the studies of this condition have been retrospective. Dissatisfactions with working conditions, family life, and love relationships are the most frequently mentioned specific instances of life dissatisfactions among coronary patients.[20,21] It has not been well-established whether this willingness to complain about the life situation is a life pattern of long standing or whether it becomes exacerbated prodromal to the clinical event.

Reaction Styles. Some researchers have not focused on basic personality traits, nor upon the personal and social events which supervene, but rather on the personal style of the psychological reactions which occur when the trait-bearing person is confronted by the challenging event. In this category of reaction style are included: emotional response, ego defenses, and coping style. A low threshold to anxiety and complaining has been reported as typical of the coronary patient, particularly the one about to develop angina pectoris.[22] Numerous studies using clinical judgments or psychological tests have shown high levels of anxiety and neuroticism in coronary patients. A few of the studies have had the advantage of being prospective. In terms of ego defense, the literature most often implicates denial and compulsive defenses as being particularly favored by coronary patients.[13] These defenses tend to be used excessively and inappropriately, particularly in response to hostile impulses. Many patients with myocardial infarction also try to deny the fact of their own illness. This is associated with delay in responding to initial symptoms as well as studied casualness in adhering to medical regimen later on.

Some persons deal with troubling situations by means of overt behavior. In this way they can bypass both unpleasant emotions and the less adaptive ego defenses. The so-called "work addict" and the high achiever who strives blindly and continuously for higher achievements may be using these behaviors as a way of coping with feelings of unworthiness or insecurity.[16]

Considerable progress has been made in the last decade in specifying those particular sociological, psychological, and overt behavioral variables which are associated with various temporal phases in the natural history of coronary disease. This work has recently been the subject of a comprehensive review.[23]

Psychosocial factors influencing use of medical care. Medical sociologists have considered that sub-cultural differences (within the total United States society) influence how physical symptoms will be experienced and defined, and these relate to the seeking of medical care.[24] There are also differences between the sexes in readiness to consider a physical discomfort as a sign of sickness. In addition to the social determinants, personality factors seem to be influential in delaying the seeking of medical aid in some men later admitted to coronary care units.[25] In view of the importance of medical intervention at the initial stages of cardiac aberrations, it is important to discover and seek to eliminate the causes of these postponements in obtaining medical care. Progress in the area could have a significant impact on the mortality rate from initial myocardial infarction.

A related issue already alluded to above is the influence of psychosocial factors on compliance with medical advice. On the one hand are the coronary patients who are sufficiently gripped by denial, rationalization, and refusal to accept the sick role during their convalescence that they fail to observe recommended diets, to cease smoking cigarettes, or to take medication in the absence of pain. On the other hand, there are those patients who embrace the sick role so strongly that they are reluctant to comply with the physician's instructions to begin modest exercise and to resume their usual social responsibilities. These persons have, in fact, become "cardiac cripples." In both these kinds of situations, psychological forces detract from the patient's chance of making a normal recovery. These issues have not been adequately studied by behavioral scientists as yet.

Unresolved Problems

Many unresolved problems in this area of research cannot be catalogued adequately here. Three major foci of such problems should be listed, however. They are the issues of conceptualization, measurement, and attitudes of other scientists.

Social and behavioral scientists studying chronic diseases have not approached their work with a common set of concepts. Definitions of terms differ from one research group to another. The occasional use of common vernacular (e.g. neuroticism) conceals both from the lay public and natural scientists the fact that in the better behavioral studies these terms have a well-specified technical meaning and are not used in their "everyday" sense. The problem of developing a common conceptual framework which will integrate both sociological and psychological concepts has not yet been adequately resolved. It could be that the studies of coronary disease done by sociologists are really quite supportive of those done by psychologists if it turns out that these two sciences are talking about related phenomena but at different levels of abstraction. These questions can only be resolved by interdisciplinary study based on an integrated conceptual framework. Another problem is the tendency for non-behavioral scientists to attempt to reduce the wide array of findings reviewed above to some single notion such as "stress." This oversimplification conceals what progress has been made towards specifying and operationalizing variables in the behavioral area. It also tends to conceal those relevant findings which fall outside the boundaries of "stress."

The second unresolved problem is that of reliable and valid measurement of those social, psychological and behavioral variables which have been found associated with atherosclerotic diseases. The fields of sociology and psychometrics have made considerable progress in the past forty years in developing measurement methodologies. This available knowledge has seldom been utilized in studies of coronary disease. This shortcoming is related in part to the failure of principal investigators of cardiovascular studies to obtain adequate consultation from appropriate professionals in these areas. For many of the psychosocial variables which are relevant to cardiovascular disease in the light of present knowledge, reliable and valid data gathering techniques have already been developed by the respective behavioral sciences. It is to be hoped that future cardiovascular studies will achieve a greater consensus in using the best of these measures. New measures will need to be constructed for those variables for which no adequate measures now exist. It will take considerable work to develop these, but the methods for such development are available.

A third problem area still unresolved relates to the understanding and acceptance of behavioral sciences by biological scientists and clinicians. Everybody is behaving all the time, and hence almost everyone perceives himself as an expert on human behavior. Because the pronouncements of self-styled experts on behavior are so often wrong, natural scientists often feel that this is an area where no science can exist. This is, of course, false. The behavioral sciences have well-developed bodies of knowledge and carefully constructed technologies. An opposite view is equally troubling, namely that the behavioral sciences can fathom all the vagaries of human behavior and come up with plans to remedy them. This uncritical optimism is also unjustified. A more constructive outlook would be somewhere between these two extremes. It would recognize that the empirical, quantitative study of human behavior is beyond its infancy as a science, but still far from maturity. Placing the social and behavioral sciences in the proper perspective will resolve some of the problems now hindering adequate incorporation of this body of knowledge into the struggle against cardiovascular disease.

Recommendations

1. Research should be encouraged which would have as its objective the standardization of the definition of key psychosocial concepts which have been found associated with cardiovascular diseases. This research should, if possible, also seek to develop conceptual frameworks which will link and interdigitate relevant concepts from the fields of sociology and psychology.

2. Given this conceptual development, research should be encouraged which will develop standard data gathering techniques which will measure the above concepts in a manner which is at once reliable, valid, and convenient.

3. Once this progress has been made in conceptualization and measurement, field studies of cardiovascular diseases should be encouraged to incorporate a wide variety of these psychological and sociological measures along with physiological and clinical variables to test for interrelations among the various domains of variables and to seek to confirm which of these psychosocial variables are indeed caught up in the etiology of atherosclerosis and its clinical sequelae.

4. The psychosocial basis of adherence or nonadherence to prescribed regimens should be studied since adherence will, in the long run, be the limiting factor in the long-term prevention of atherosclerosis.

References

1. Gordon T, Verter J: Serum cholesterol, systolic blood pressure and Framingham relative weight as discriminators of cardiovascular disease. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Edited by WB Kannel, T Gordon. US Dept of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Section 23. Washington DC, Government Printing Office.

2. Bernstein DA: Modification of smoking behavior: An evaluative review. Psychol Bull 71:418-440, 1969

3. Dwyer JT, Feldman JJ, Mayer J: The social psychology of dieting. J Health Soc Behav 11:269-287, 1970

4. McGinn NF, Harburg E, Julius S, et al: Psychological correlates of blood pressure. Psychol Bull 61:209-219, 1964

5. Jenkins CD, Hames CG, Zyzanski SJ, et al: Psychological traits and serum lipids: I. Findings from the California Psychological Inventory. Psychosom Med 31:115-128, 1969

6. Harlan WR, Oberman A, Mitchell RE, et al: Constitutional and environmental factors related to serum lipid and lipoprotein levels. Ann Intern Med 66:540-555, 1967

7. Syme SL, Borhani NO, Buechley RW: Cultural mobility and coronary heart disease in an urban area. Amer J Epidem 82:334-346, 1965

8. Shekelle RB, Ostfeld AM, Paul O: Social status and incidence of coronary heart disease. J Chronic Dis 22:381-394, 1969

9. Friedman M, Rosenman RH: Association of specific overt behavior pattern with blood and cardiovascular findings: Blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. JAMA 169:1286-1296, 1959

10. Rosenman RH, Friedman M, Straus R, et al: Coronary heart disease in the Western Collaborative Group Study: A follow-up experience of 4-1/2 years. J Chronic Dis 23:173-190, 1970

11. Keith RA, Lown B, Stare FJ: Coronary heart disease and behavior patterns: An examination of method. Psychosom Med 27:424-434, 1965

12. Caffrey B: Behavior patterns and personality characteristics related to prevalence rates of coronary heart disease in American monks. J Chronic Dis 22:93-103, 1969

13. Van der Valk JM, Groen JJ: Personality structure and conflict situations in patients with myocardial infarction. J Psychosom Res 11:41-46, 1967

14. Lovell RRH, Verghese A: Personality traits associated with different chest pains after myocardial infarction. Brit Med J 3:327-330, 1967

15. Jenkins CD, Zyzanski SJ, Rosenman RH: Progress toward validation of a computer-scored test for the type A coronary-prone behavior pattern. Psychosom Med 33:193-202, 1971

16. van Heijningen HK, Treurniet N: Psychodynamic factors in acute myocardial infarction. Int J Psychoanal 47:370-374, 1966

17. Sales SM: Organizational role as a risk factor in coronary disease. Adm Sci Quart 14:325-336, 1969

18. Russek HI: Stress, tobacco, and coronary disease in North American Professional Groups: Survey of 12,000 men in 14 occupational groups. JAMA 192:189-194, 1965

19. Bruhn JG, McCrady KE, du Plessis A: Evidence of "emotional drain" preceding death from myocardial infarction. Psychiat Dig 29:34-40, 1968

20. Liljefors I, Rahe RH: An identical twin study of psychosocial factors in coronary heart disease in Sweden. Psychosom Med 32:523-542, 1970

21. Blohmke von M, Schaefer H, Abel H, et al: Medizinische und soziale Befunde bei koronaren Herzkrankheiten. Munchen Med Wschr 111:701-710, 1969

22. Ostfeld AM, Lebovits BZ, Shekelle RB, et al: A prospective study of the relationship between personality and coronary heart disease. J Chronic Dis 17:265-276, 1964

23. Jenkins CD: Psychologic and social precursors of coronary disease. New Eng J Med 284:244-255, 307-317, 1971

24. Zola IK: Culture and symptoms--an analysis of patients' presenting complaints. Amer Sociol Rev 31:615-630, 1966

25. Hackett TP, Cassem NH: Factors contributing to delay in responding to the signs and symptoms of acute myocardial infarction. Amer J Cardiol 24:651-658, 1969

I. MULTIPLE RISK FACTORS

Current State of Knowledge

The greater the number of risk factors in a given individual the more apt he is to manifest arteriosclerosis or its complications. Evidence for this has been attained from the Framingham Study[1] and from the data of the National Cooperative Pooling Project.[2] In Figure 1 are shown data from that study for three major risk factors: serum cholesterol over 250 mg. per ml., diastolic blood pressure of 90 mm. Hg. or more, and smoking smoking. Individuals with all three risk factors had age-adjusted rates of first coronary events more than eight times that of individuals with none of these factors. With two risk factors the rate was increased by more than four-fold over those with none, and with one risk factor it was more than twice that in those with none. The Framingham Study showed an even greater effect of the presence of multiple risk factors.

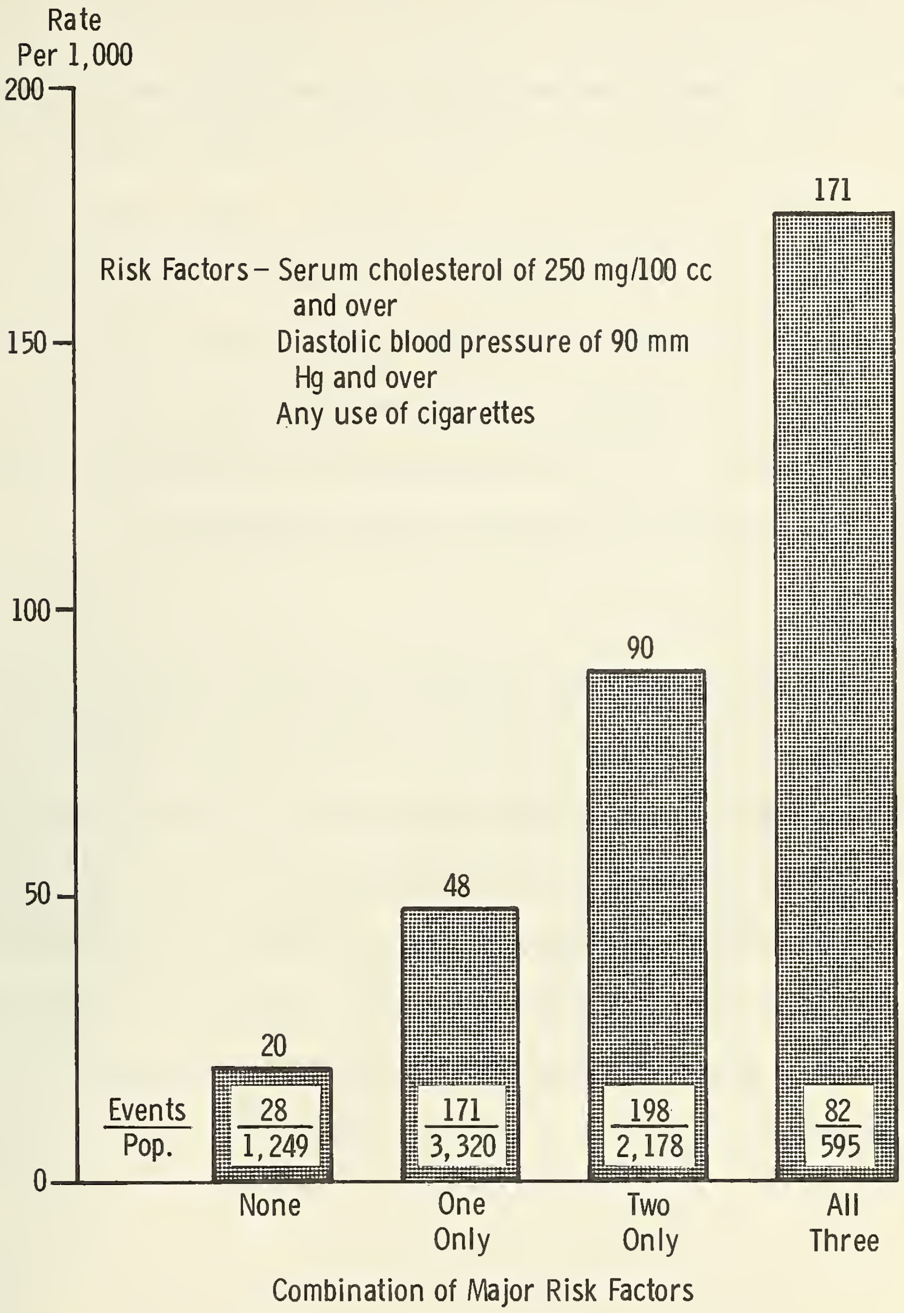
Since all of these risk factors are susceptible to modification, it seems that intervention in populations with multiple risk factors might prove especially effective, and some preliminary studies are consistent with this hypothesis. The Task Force convened a panel of experts to consider a trial intervention in such high risk individuals. The panel concluded that such trials would be feasible. Similar trials are also in different stages of planning or in operation in European countries under the auspices of the World Health Organization.

Unresolved Problems

Despite evidence that combinations of risk factors increase the risk

FIGURE 1

COMBINATION OF RISK FACTORS AT ENTRY AND AGE-ADJUSTED RATES* OF FIRST MAJOR CORONARY EVENT FOR WHITE MALES AGE 30-59 AT ENTRY. NATIONAL COOPERATIVE POOLING PROJECT



*Rates for 10 Years of Followup Adjusted by Age to the U. S. White Male Population, 1960.

of arteriosclerosis and its complications there is, as yet, no conclusive evidence that intervention with respect to normalizing these risk factors will reduce the risk of arteriosclerosis. Not all investigators share this confidence in the primary pathogenetic role of the risk factors that have been identified to date and a lowering of risk by multiple intervention would provide proof of the risk factor hypothesis. While such a study appears to be feasible in terms of the size of the study population, there are numerous problems in interpreting the results. Such a study would not answer questions as to specific risk factors. In fact, the outcome might well be determined by alteration of only a single one of the risk factors. Furthermore, problems of adherence are increased because of the multiplicity of therapeutic measures. It is not known whether the necessity to control multiple risk factors will increase or decrease adherence.

Recommendation

The Task Force recommends that the National Heart and Lung Institute develop and support trials in high risk subjects with multiple risk factors (elevated blood lipids, hypertension, and cigarette smoking). Although such trials will not define the contribution of each factor separately, they will determine the value of intervention on several factors in much the same way that the practicing physician must cope with the problem. Moreover, a trial with respect to multiple factors affords the advantage of study populations of manageable proportions.

References

1. Gordon T, Sorlie P, Kannel WB: Coronary heart disease, atherothrombotic brain infarction, intermittent claudication--A multivariate analysis of some factors related to their incidence: Framingham Study, 16-year follow-up. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Edited by WB Kannel, T Gordon. US Dept of Health, Education, and Welfare, Public Health Service, NIH, Section 24

2. Inter-Society Commission for Heart Disease Resources: Atherosclerosis Study Group and Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42:A55-A95, 1970

J. STATEMENT TO THE PUBLIC ON RISK FACTORS

The Task Force endorses the following statement to the public with regard to risk factors:

Epidemiological and laboratory studies have uncovered several factors which are associated with an increased risk of developing atherosclerotic heart disease and other manifestations of arteriosclerosis. Elevated serum lipids, high blood pressure, and cigarette smoking are major controllable risk factors.

It is not known whether all of these risk factors are causally related to ather sclerotic cardiovascular diseases but the best judgment from present knowledge indicates that a significant reduction in the incidence of these diseases may be achieved by observing the following guidelines:

Blood Lipids (cholesterol and triglycerides): Elevation of serum lipids is implicated in the etiology of arteriosclerotic disease. Current data indicate that the average North American has higher than optimal blood lipid levels and ingests excessive calories, saturated fat, and cholesterol. Pending confirmation by appropriate diet or drug trials, it therefore would appear prudent for the American people to follow a diet aimed at lowering serum lipid concentrations. For most individuals, this can be achieved by lowering intake of calories, cholesterol, and saturated fats. An attempt should be made to attain and maintain optimal weight through weight loss by balancing caloric intake and expenditure. In certain individuals with clearly elevated levels of serum cholesterol or triglycerides, close medical supervision with more vigorous attention to the diet and the use of drugs may be necessary.

High Blood Pressure: There is conclusive evidence that control of elevated blood pressure by appropriate drugs decreases the occurrence of important complications of arteriosclerotic disease. Treatment of hypertension should be early, carefully regulated, and sustained under medical supervision.

Cigarette Smoking: Since cigarette smoking has been demonstrated to be an important risk factor in arteriosclerotic disease, all smokers should be urged to stop. Young people should be vigorously deterred from starting to smoke.

IV. PRESYMPTOMATIC ATHEROSCLEROTIC DISEASE

A. CORONARY

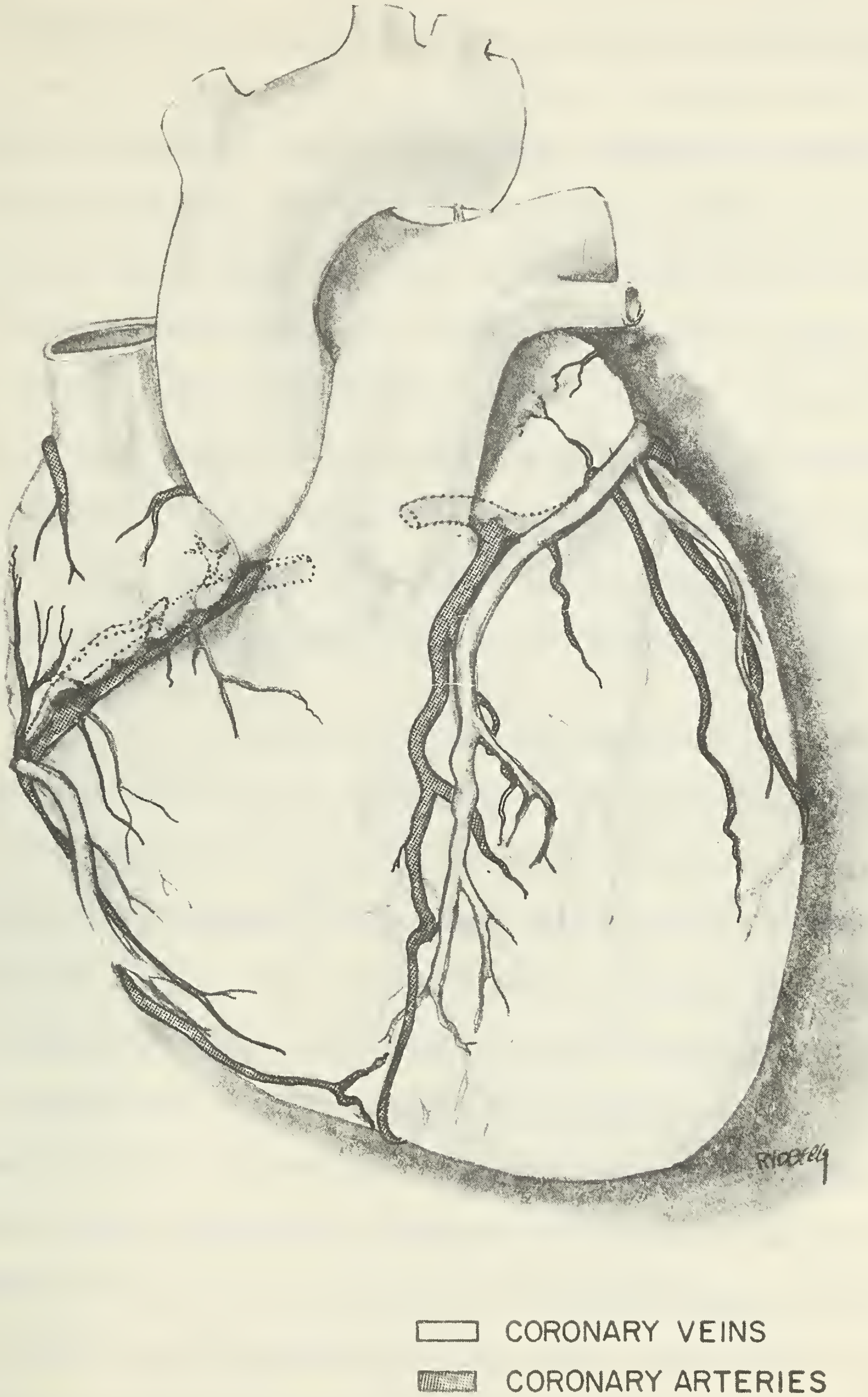
Current State of Knowledge

As detailed elsewhere in this report, diseases of the coronary arteries develop early in life. By early adulthood, macroscopic lesions of the coronary arteries are relatively common, as shown by studies of the hearts of young men killed accidentally or in combat.[1,2] Such lesions are rarely of sufficient magnitude to cause symptoms, abnormal physical findings, electrocardiographic abnormalities, or changes in ventricular dynamics until much later in life. Two factors explain a substantial part of this apparent paradox: 1) blood flow through an artery is not materially diminished by atherosclerotic plaques until the lumen has been decreased by more than 50 percent; 2) as coronary occlusion gradually progresses, collateral circulation is augmented. In the absence of major occlusive disease, the connections that exist among the coronary arteries are of very small size, with lumen diameters ranging from 20 to 350 microns.[3] If occlusive disease occurs, a rich network of collateral circulation may develop such that a major artery may be completely occluded without causing clinically recognized myocardial infarction. The size and location of the occluded vessel and the size of occlusion within the vessel, i.e., at its origin, mid or terminal portion also determine the clinical manifestations. In almost every instance of myocardial infarction or sudden death due to coronary heart disease, there is evidence of severe and chronic atherosclerotic stenosis of one or more of the major coronary arteries (Figure 1).

Since the first recognized manifestation of coronary artery heart disease may be sudden death or massive myocardial infarction, it is evident that

FIGURE 1

The Vascular System of the Heart



"asymptomatic" severe coronary atherosclerosis is common and of major importance. The frequency of dangerous coronary arterial lesions is not known for Americans at any age. In part, this deficit in information reflects the lack of agreement between investigators as to what type of lesion should be considered as being clinically significant. Another problem is the fact that representative samples of the population have not been studied, either in life or after death, by methods adequate to provide the necessary information. It has been believed by some that any plaque, occlusive or not, must be regarded as being of potential clinical importance since it may form the site for an acute coronary thrombosis. However, in one recent study by coronary arteriography of patients with angina pectoris it was shown that death due to coronary artery heart disease was very unlikely during a 5-year period of follow-up unless there was severe occlusive disease of more than one of the three major coronary arteries.[4]

The problem is made more complex by the lack of correlation between symptoms noticed by the patient and objective evidence, not only of coronary arterial lesions, but also of the resulting structural damage to the heart muscle. Thus, in the Framingham experience[5] approximately 25 percent of all acute myocardial infarctions were clinically "silent," i.e., were not accompanied by severe pain or other symptoms that lead to diagnosis or to hospitalization. The diagnosis in these persons was established by electrocardiographic changes developing in the interim between routine follow-up examinations. Moreover, the discomfort of transient and reversible myocardial ischemia (angina pectoris) is frequently misinterpreted as indigestion, bursitis, muscle pain, arthritis, or esophageal spasm by the patient or his physician. A meticulous medical history properly analyzed will usually allow the correct diagnosis to be made. Nevertheless, these uncertainties imply that the terms "presymptomatic" or "asymptomatic" coronary artery heart disease also include those individuals with symptoms of myocardial ischemia who are misdiagnosed as having a benign disorder.

Methods of Detection. Early detection of asymptomatic ischemic heart disease is clearly of major importance. Persons who realize that they have heart disease are more likely to protect themselves against potentially dangerous overactivity. They are more likely to reduce weight, stop smoking, and have effective treatment of hypertension and hyperlipidemia. A large number of diagnostic measures have been applied to the problem of early detection of coronary artery heart disease. All are limited by the physiological problems already described, as well as by other factors such as expense, hazard of the test procedures and uncertain merit.

1. Analysis of symptoms. As described above, not all patients with undiagnosed coronary artery heart disease are truly asymptomatic and an undefined percentage of such persons may be detected by a careful analysis of symptoms. In a study of Western Electric Company employees Paul[6] et al. found significant development of clinical coronary disease in men who had a history of chest discomfort not adequate for a diagnosis of angina pectoris at initial examination. Other investigators have devised computer based, statistically weighted questionnaires for this purpose. However, neither the sensitivity nor the specificity of this approach has as yet been adequately evaluated.

2. Physical examination. Although an occasional, asymptomatic person

may have physical findings consistent with, or even suggestive of, coronary artery heart disease(e.g., cardiomegaly, mitral regurgitation,gallop rhythm, abnormal splitting of heart sounds, or abnormal precordial impulses), such findings are not recognized with sufficient frequency to make these important in population research. However, they may be of great significance to the individual, if present.

3. Electrocardiography. Persons with angina pectoris who have not sustained prior myocardial infarction characteristically have electrocardiograms recorded at rest that are within normal limits. Many of these recordings are truly indistinguishable from those of completely healthy people taken under similar circumstances. Others have "minor" electrocardiographic variations that are similar to those seen in a relatively small percentage of apparently healthy people. But recent longitudinal population studies have provided evidence that such minor changes may have prognostic significance for the future development of coronary artery heart disease. In the community study of Framingham, Massachusetts, persons with such "non-specific" electrocardiographic changes as flattened or inverted T-waves in certain electrocardiographic leads had a significantly greater likelihood of subsequent development of heart disease than did persons without these changes.[7] It should be recognized, however, that such changes are indeed non-specific, relatively insensitive, and serve only to classify individuals into population groups with some increased hazard of subsequent development of heart disease. These changes do not allow the diagnosis of heart disease to be made in any individual.

In contrast, individuals with typical electrocardiographic changes of prior myocardial infarction have a very strong probability of having occlusive lesions of major coronary arteries and major scars in the ventricular myocardium. Kannel, et al[5] have reported that asymptomatic persons developing such electrocardiographic changes between sequential examinations have the same life expectancy as persons with the typical clinical history of a documented myocardial infarction.

Methods for recording the electrocardiogram for periods of several hours utilizing a portable electromagnetic tape recorder have been developed. Serious abnormalities of cardiac rhythm may be discovered in apparently healthy individuals. These disturbances of rhythm may be evidence of serious heart disease, having important prognostic implications.

4. Stress electrocardiography. The electrocardiogram recorded after applying stress to the cardiovascular system has been used for many years as a diagnostic aid in the evaluation of patients with chest pain. Many different types of stress tests have been studied, but the stress of muscular exercise has proved most useful.[8] The ability of the exercise electrocardiographic test to identify individuals with overt coronary heart disease depends upon the type of test performed and the electrocardiographic criteria applied. The sensitivity of this test as it is usually performed and interpreted, the standard two-step test, is approximately 60 percent.[9] Recent studies have indicated that the sensitivity can be increased significantly without loss of specificity if exercise of maximal or near maximal severity is employed.[9,10] In addition, it appears that use of the digital computer will allow increased precision of diagnosis.[11,12,13]

Several studies[14,15] have indicated that exercise testing of apparently healthy persons will result in a significant number of abnormal electrocardiographic responses. Such "positive" responses are rare in persons under the age of 40 years, the prevalence increasing with advancing years to approximately 20 percent positive responses in the 6th decade to exercise of near maximal severity.[15] There is evidence that such responses may have important prognostic implications. According to recent data[16] during a longitudinal population study, the probability of developing clinical coronary atherosclerotic heart disease (angina pectoris, myocardial infarction, or sudden death) within 5 years is approximately 85 percent in individuals developing a positive exercise test. It should be noted that the exercise utilized in this study was of only moderate severity, i.e., a treadmill walk at 3 m.p.h. on a grade of 5 percent with a duration of 10 minutes. The yield of positive electrocardiographic responses to exercise in this study of middle-aged asymptomatic men was approximately 4 percent.

These data are in general accord with earlier studies.[17-21] It is possible to utilize the exercise electrocardiogram to identify a group of asymptomatic men at greater risk of developing clinical coronary artery heart disease than the population at large or those with a negative electrocardiogram.

5. Hemodynamic measurements. There is strong evidence from many studies that persons with symptomatic coronary artery heart disease tend to have abnormalities of cardiac output, left ventricular end-diastolic pressure, rate of ejection, ejection fraction, and left ventricular mass. It is

probable that many persons with presymptomatic disease will also manifest such changes. However, direct measurement of these variables requires intracardiac catheterization and angiocardiography, procedures that are not feasible for large scale application. A number of atraumatic or noninvasive procedures that reflect certain of these hemodynamic abnormalities have been utilized in the study of persons with or at risk of coronary artery heart disease. These include the ballistocardiogram, kinetocardiogram, systolic time intervals, echocardiogram, and apex cardiogram. Of these promising methods, only the ballistocardiogram has been utilized in longitudinal studies of significant duration and size. Starr[22] has reported that asymptomatic persons with abnormal ballistocardiograms have a much greater risk of subsequent development of heart disease than do persons without such abnormality. A more recent study has confirmed and extended these results.[23]

6. Coronary angiography. The most precise method of detecting occlusive disease of the large coronary arteries during life is by selective injection of the ostia of these vessels with radio-opaque media and simultaneous recording on cine-fluorographic or X-ray film.[24,25,26] This procedure carries a small but definite risk, and is expensive. Although coronary angiography is impractical for large-scale screening, it is a powerful tool for accurate diagnosis in properly selected persons. Thus it provides an excellent, though not perfect modality of diagnosis, against which the various noninvasive methods, including the exercise electrocardiogram, the ballistocardiogram, etc., may be checked.[27,28]

Unresolved Problems

A major unresolved problem is the prognostic significance of the coronary artery lesions seen at coronary angiography or at postmortem examinations. As pointed out elsewhere in this report, a wide spectrum of lesions may be recognized by careful pathological examination ranging from the "fatty streak" to complete or near complete occlusion by the atheromatous plaques. If the coronary angiographic observations by Friesinger, et al[4], are confirmed by other and more extended investigations, it would appear that only severely occluded large coronary arteries constitute a major hazard with respect to early death from heart attack. The implication of lesser stenosis over long periods of time has not been evaluated. This important question can be approached by long-term prospective studies involving patients undergoing coronary angiography. It can also be approached by meticulous pathological examination of all persons dying from possible coronary artery heart disease, including those due to sudden death. Improved methods for characterization of the coronary arterial tree and for detection of early stages of myocardial necrosis would be required.

Another major problem is the development of sensitive and accurate methods for the early detection of significant coronary artery heart disease that can be applied with safety and economy to a large segment of the population. Screening techniques are needed for middle-aged persons, especially men, that would detect the majority of those with major occlusive disease of large coronary arteries. It is possible, but as yet unproven, that only modest refinements of existing techniques would be adequate, especially if coupled with accurate, non-biased methods of analysis of the information. Problems in need of solution include those relating to instrumentation and automation of analytical procedures.

The optimal type of stress utilized with the electrocardiogram (or with the other measurements) has not been clearly defined. It is to be recognized that exercise testing of middle-aged and older men carries with it a small but definite hazard and because of other disorders, such as orthopedic disability, not all persons can be exercised by the walking or climbing tests generally utilized. There is no agreement as to severity or duration of exercise required. Other forms of potentially useful stress including the "isometric hand grip" test and various types of pharmacologic stress have not been adequately evaluated.

It is possible to envision other methods for the study of the adequacy of the coronary circulation that have not yet been applied clinically nor brought to this level of development. It is not yet possible to visualize the coronary arterial tree in life except by angiography, and this method is not applicable to screening of a large population. Lack of a method to accomplish direct visualization on a large scale is a major unresolved problem.

As in the other stages of coronary disease, treatment in the asymptomatic phase remains in a highly unsatisfactory state. There is some evidence that cessation of smoking, treatment of hypertension, reduction in hyperlipidemia, control of obesity, and possibly an increase in physical activity will decrease the overall death rate. However, the magnitude of the reduction in overall death rate or in morbidity has not been adequately documented. Some methods of achieving these goals are promising while others remain highly unsatisfactory. Even in persons with symptomatic heart disease, it is not easy to control obesity, smoking, hyperlipidemia or hypertension.

Recommendations

1. Properly designed epidemiological studies should be carried out to determine the prevalence of potentially important but unrecognized coronary artery heart disease in an apparently well population.

2. Support should be given to the further development and understanding of the various noninvasive methods of studying cardiac function applicable to the detection of "presymptomatic coronary atherosclerotic heart disease."

The sensitivity and specificity of the following tests for the detection of coronary artery heart disease should be determined: medical history (automated), physical examination (augmented by phonocardiography), the electrocardiogram at rest and during stress, systolic time intervals, apex cardiography, kinetocardiography, ballistocardiography, and echocardiography. Consideration should be given to the utilization of coronary angiography as the "standard" against which the other indirect methods could be assayed. In addition adequate prospective studies should be made to determine the prognostic value of the various tests, singly or in appropriate combinations.

Particular attention should be given to the refinement of electrocardiographic exercise testing: automation of analysis, determination of optimal severity and duration of exercise, and identification of optimal lead systems. Optimal criteria for a positive test should be defined. Special consideration should be given to the combined utilization of electrocardio-

graphic stress testing and non-invasive methods for assessment of hemodynamic function in the detection of "presymptomatic coronary artery heart disease." Methods for automated recording and analysis of the ballistocardiogram, kinetocardiogram, echocardiogram, and the systolic time intervals, not only at rest but during stress, should be originated. The optimal type of stress should be defined. It is possible that stress could be applied either as exercise, (leg or hand grip) by cardiac pacing or by pharmacologic intervention.

3. Safe methods for definition of the lumen of the coronary arteries *in vivo*, that are suitable for mass application should be developed.

4. Consideration should be given to the feasibility of establishment of a special section of the Prevention Centers (recommended elsewhere in this report) for the express purpose of developing, refining and evaluating methods for the early detection of coronary atherosclerotic heart disease.

References

1. Enos WF, Holmes RH, Beyer J: Coronary disease among United States soldiers killed in action in Korea: Preliminary report. JAMA 152: 1090-1093, 1953

2. McNamara JJ, Molot MA, Stremple JF, et al: Coronary artery disease in combat casualties in Vietnam. JAMA 216:1185-1188, 1971

3. Baroldi G, Mantero O, Scomazzoni G: The collaterals of the coronary arteries in normal and pathological heart. Circ Res 4:223-228, 1956

4. Friesinger GC, Page EE, Ross RS: Prognostic significance of coronary arteriography. Trans Ass Amer Physicians 83:78-91, 1970

5. Kannel WB, McNamara PM, Feinleib M, et al: The unrecognized myocardial infarction: Fourteen-year follow-up experience in the Framingham Study. Geriatrics 25:75-87, 1970

6. Paul O, Lepper MH, Phelan WH, et al: A longitudinal study of coronary heart disease. Circulation 28:20-31, 1963

7. Dawber TR, Kannel WB: The early diagnosis of coronary heart disease. Presymptomatic Detection and Early Diagnosis. London, Pitman Medical Publishing Co Ltd, 1968, pp 257-281

8. Simonson E: Electrocardiographic stress tolerance tests. Prog Cardiovasc Dis 13:269-292, 1970

9. Sheffield LT, Reeves TJ: Graded exercise in the diagnosis of angina pectoris. Mod Conc Cardiovasc Dis 34:1-6, 1965

10. Bruce RA, Hornsten TR: Exercise stress testing in evaluation of patients with ischemic heart disease. Prog Cardiovasc Dis 11: 371-390, 1969

11. Sheffield LT, Holt JH, Lester FM, et al: On-line analysis of the exercise electrocardiogram. Circulation 40:935-944, 1969

12. Bruce RA, Mazzarella JA, Jordan JW Jr, et al: Quantitation of QRS and ST segment response to exercise. Amer Heart J 71:455-466, 1966

13. Blomqvist G: The Frank lead exercise electrocardiogram: A quantitative study based on averaging technic and digital computer analysis. Acta Med Scand Suppl 440:5-98, 1965

14. Riley CP, Oberman A, Lampton TD, et al: Submaximal exercise testing in a random sample of an elderly population. Circulation 42:43-52, 1970

15. Doan AE, Peterson DR, Blackmon JR, et al: Myocardial ischemia after maximal exercise in healthy men: A method for detecting potential coronary heart disease? Amer Heart J 69:11-21, 1965

16. Doyle JT, Kinch SH: The prognosis of an abnormal electrocardiographic stress test. Circulation 41:545-553, 1970

17. Robb GP, Marks HH: Post exercise electrocardiogram in arteriosclerotic heart disease: Its value in diagnosis and prognosis. JAMA 200: 918-926, 1967

18. Brody AJ: Master two-step exercise test in clinically unselected patients. JAMA 71:1195-1198, 1959

19. Franco SC, Gerl AJ, Murphy GT: Periodic health examinations: A long term study, 1949-1959. J Occup Med 3:13-20, 1961

20. Rumball A, Acheson ED: Latent coronary heart disease detected by electrocardiogram before and after exercise. Brit Med J 1:423-428, 1963

21. Bellet S, Roman LR, Nichols GJ, et al: Detection of coronary-prone subjects in a normal population by radioelectrocardiographic exercise test: Follow-up studies. Amer J Cardiol 19:783-787, 1967

22. Starr I: Prognostic value of ballistocardiograms; as judged by after-histories of 211 healthy persons and 221 patients followed from 5 to 25 years. Ballistocardiography and Cardiovascular Dynamics: Proceedings of the First World Congress on Ballistocardiography and Cardiovascular Dynamics. Edited by AA Knoop. Baltimore, Williams & Wilkins Company, 1966, pp 7-20

23. Baker BM, Scarborough WR, Davis FW Jr, et al: Ballistocardiography and ischaemic heart disease: Predictive considerations and statistical evaluation. Proc Roy Soc Med 60:1290-1297, 1967

24. Sones FM, Shirey EK, Proudfit WL, et al: Cine-coronary arteriography. Proceedings of the 32nd Scientific Sessions of the American Heart Association, October 23-25, 1959. Circulation 20:773-774, 1959

25. Paul S: Coronary angiography: A technical, anatomic and clinical study. Acta Radiol Suppl 233:5-215, 1964

26. Judkins MP: Percutaneous transfemoral selective coronary arteriography. Radiol Clin N Amer 6:467-492, 1968

27. Kattus AA, MacAlpin R, Longmire WP, et al: Coronary angiograms and the exercise electrocardiogram in the study of angina pectoris. Amer J Med 34:19-41, 1963

28. Roitman D, Jones WB, Sheffield LT: Comparison of submaximal exercise ECG test with coronary cineangiocardiogram. Ann Intern Med 72: 641-647, 1970

B. CEREBRAL

Current State of Knowledge

The atherogenic process in the cerebral arteries is similar to that of other vascular beds. However, there are a number of features which distinguish this vascular bed and the effects of atherosclerosis upon it from other arteries. Some of these have been identified as risk factors unique to the cerebral circulation.

The Configuration of the Arteries. The arteries supplying the brain arise from the aortic arch (the brachiocephalic and the left common carotid arteries) and the subclavian arteries (right and left vertebral arteries). In a significant percentage of people the anatomical configuration of these vessels varies from the typical. For example, a frequent anomaly is the origin of the left common carotid artery from the brachiocephalic artery. In this case the blood flowing into three of the four arteries supplying the brain, both carotids and the right vertebral, must first course through a single brachiocephalic trunk. This anatomical configuration, laid down during embryogenesis, may predispose the patient to symptomatic cerebrovascular disorder during middle age.

In a similar manner other congenital variations may protect or predispose the individual to stroke[1] (Figures 1 and 2). Some of these are:

1) origin of the left vertebral artery from the aortic arch
2) the extent of anatomic connections between the two carotid and/or the two vertebral systems
3) the pattern of the circle of Willis and the caliber of its connecting links

FIGURE 1

Arteries Supplying the Brain

Reproduced with the permission of the publishers and the authors from Cerebrovascular Disorders, James F. Toole and Aneel N. Patel, McGraw-Hill Co., 1967, pg 1.

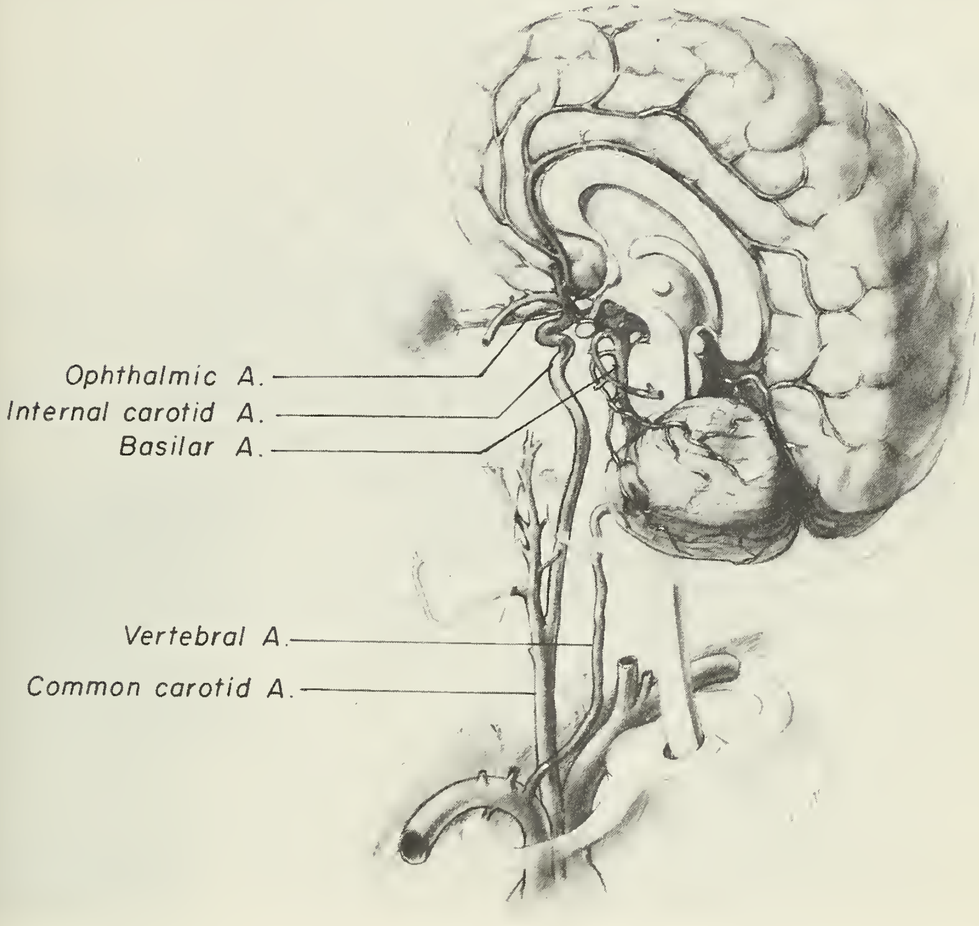
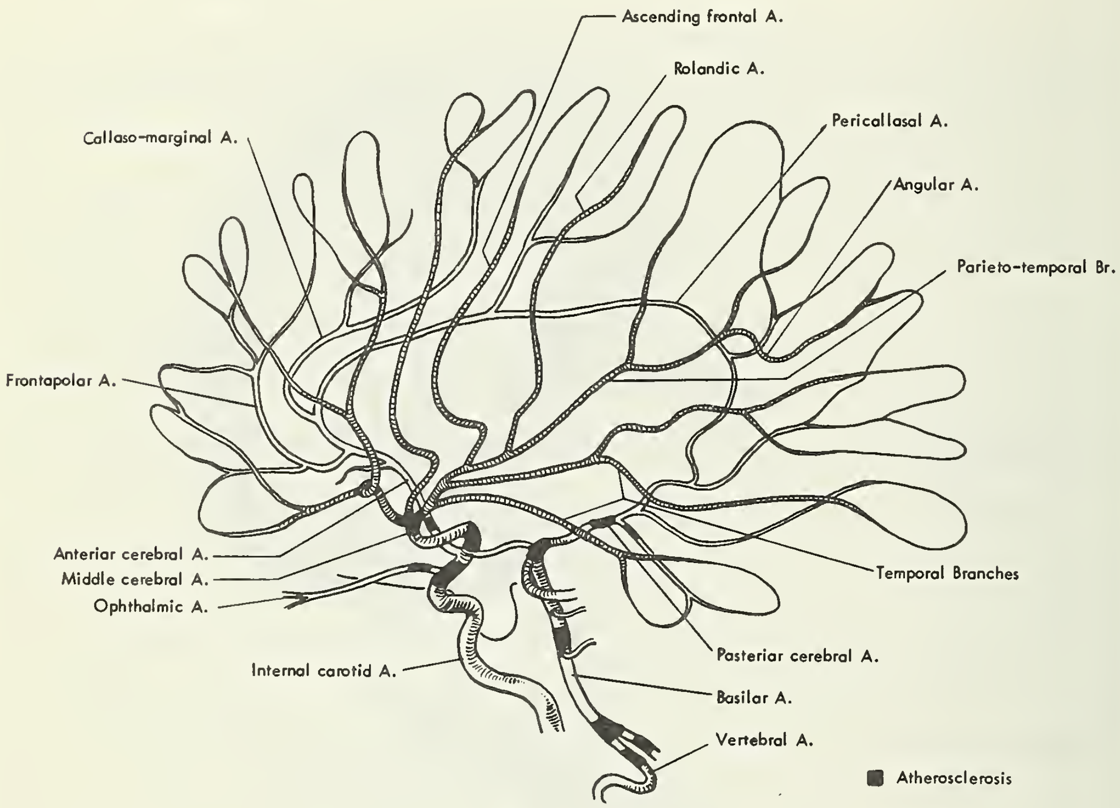


FIGURE 2

Atherosclerosis of Arteries Supplying the Brain

Atherosclerosis involving the intracranial arteries is a patchy disease affecting primarily junctions, bifurcations, angulations and points of branching of the major arteries. The extent to which these plaques affect regional cerebral blood flow depends upon the anastomoses with which the patient is born or the collaterals which he can develop during life.



4) the anastomotic connections of the terminal branches of the large surface conducting arteries over the brain
5) aneurysmal dilatations of the intracranial arteries
6) arteriovenous malformations.

Variation in Vascular Beds within the Individual. Coronary atherosclerosis usually becomes symptomatic approximately 10 years before cerebral, despite the fact that the latter supplies an organ more exquisitely sensitive to impairment of blood flow. It is thought that this is due to the hydrostatic pressure, causing cerebral arterial pressure in upright man to be lower than the pressure in the coronary arteries. In fact, however, the reasons are unknown.[1]

Murmurs in the Neck or Head. Arterial bruits heard over the neck or head of adults suggest atherosclerotic cervicocranial vascular disease.[2-9] Whether this has predictive value in the asymptomatic population is unknown.

Age. The incidence of cerebral infarction and hemorrhage mounts with age but the causative factors change. In the young, infarction is usually the result of arteritis or embolism from the heart, while in the adult it is due to atherosclerosis.[10] Below age 50 cerebral hemorrhage is generally the result of blood dyscrasia, vascular anomaly, or ruptured aneurysm while above 50, spontaneous cerebral hemorrhage is usually caused by sustained hypertension.

Sex. Some epidemiological surveys have shown an apparent male preponderance for cerebral infarction in certain age groups but not in others.[11-13]

The reasons are unknown but have been variously attributed to differences in hormones, life stress, hypertension, smoking and diet. Other investigators [14,15] have questioned this apparent difference in predilections in the two sexes for stroke.

Blood Lipids. Elevations in cholesterol and triglyceride-rich pre-β lipoprotein found in subjects under age 50 are associated with increased risk of cerebral infarction, the risk varying with the degree of associated hypertension. However, at the present time there is only weak evidence, not yet statistically significant, associating cerebral infarction with abnormalities in blood lipids in populations above age 50.[13,16]

Hypertension. High blood pressure sustained for long periods of time is one of the most important factors which increases the risk of cerebral infarction and hemorrhage.[17-21] It accelerates the atherogenetic process in the large arteries, increases complicated lesions, and predisposes to cerebral infarction. In addition, arterial hypertension causes changes in small arteries and in arterioles leading to hyaline thickening, aneurysmal dilatations, and eventually to occlusion or rupture of these small vessels. These in turn result in multiple micro-infarctions (lacunar state)[1] or in cerebral hemorrhage.

Prospective epidemiological studies have shown hypertension to be the single most reliable predictor for the different varieties of strokes.[22] Even moderate hypertension found by single blood pressure determination in either sex at any age is associated with increased risk of stroke.[23,24] When the measurement is associated with evidence of prolonged sustained hypertension (i.e., left ventricular enlargement on electrocardiogram or chest X-ray), the risk of cerebral infarction or hemorrhage is more than five times that of a comparable normotensive population.[13-23] Consequently, asymptomatic hypertensive individuals must be recognized early and treated vigorously and effectively if end-stage cerebrovascular disorders are to be prevented.

Heart Disease. Underlying heart disease (valvular lesions, myocardial infarction, cardiac dysrhythmias, conduction defects, and cardiac decompensation) are associated with greatly increased risk of cerebral infarction due to atherothrombosis and embolism.

Electrocardiographic evidence of coronary artery disease is associated with almost five-fold increased risk of cerebral infarction, left ventricular hypertrophy secondary to hypertension with a three-fold increase, and cardiac decompensation with three-fold increase in risk.[13,23,25] Furthermore hypertensive subjects who develop electrocardiographic change have nine times the risk of cerebral infarction compared to that of a normotensive population with normal electrocardiograms.

Racial and Geographic Factors. The incidence of hemorrhagic and ischemic stroke is higher in some populations than in others.[15,26-31] The reasons for this are unknown. Some seem to be genetic while others are undoubtedly the result of environmental influence. For example, native Japanese have a high incidence of cerebral hemorrhage but a low incidence of ischemic infarction.[12,32,33] In Hawaii, the proportion among the Japanese population is about equal, while in U.S. born Japanese the reverse is true. Furthermore, this striking difference seems to be changing with time, so that within the past few years in Japan the incidence of hemorrhage seems to be declining while that of infarction is mounting.[31] Some attribute this apparent change to differences in classifying deaths due to strokes while others suggest that better control of hypertension is the explanation.[15] Whatever the cause, the fact remains that there is important information to be gained from epidemiologic studies of a global nature.

Furthermore, in the continental United States there are striking differences in the incidence and prevalence of stroke among subgroups.[34,35] For instance, in whites and Negroes, both male and female, all forms of stroke are more common in the southeastern than in other parts of the United States while they are lowest in incidence and prevalence in the Rocky Mountain states. In addition, within single geographic regions there are differences in the average age of occurrence of stroke between Negro and white populations and between the two sexes.

Diabetes Mellitus. Persons with overt diabetes mellitus have a greatly increased risk of cerebral infarction.[23] It is possible but unproven that good control may reduce this risk.

Tobacco. Smoking of cigarettes increases the risk of cerebral infarction in certain population groups. (See Section on Smoking)

Obesity. Data linking excess body weight with propensity to stroke are inconclusive, except through the association with hypertension and diabetes mellitus.[23]

Blood Uric Acid. Patients with gout have an increased risk of cerebral infarction. The possible predictive value of elevated blood uric acid levels in asymptomatic individuals is not known. It has been suggested that the apparent relationship is really attributable to the association of an elevated uric acid with hypertension, obesity, and elevated blood lipids.[23]

Antiprogestational Agents. The use of certain oral contraceptive medications is accompanied by an increased risk of cerebral infarction in women who have a personal or family history of migraine.[36,37] However, there is no compelling evidence to indicate that the general population of women using these agents who are asymptomatic, normotensive, and non-diabetic are at increased risk.

Abnormalities in Blood Constituents. Persons with polycythemia vera and erythrocytosis, as well as those with other causes of increased blood viscosity, have an increased risk of cerebral infarction.[10]

Psychosocial Factors. Paffenbarger et al have demonstrated predictors for stroke which seem to relate to personality pattern, work and possibly life style.[38-40]

Seasonal Changes. The incidence of cerebral infarction is lower in summer than in winter months.[41]

Unresolved Problems

There has been investigation of the radiographic anatomy of the aortocervicocranial arteries and extensive studies of the circle of Willis. However, there has been very limited interest in and investigation of the probability that the anatomy of this arterial tree may be a critical factor in determining whether a person will develop symptomatic cerebrovascular disease and in determining the manifestations of the disease.

The reasons for the variation in incidence and prevalence rates of cerebral infarction and hemorrhage among racial groups and in different geographic regions are mysterious. The explanation of this problem will undoubtedly be the key to stroke prevention. Among the considerations are hereditary, endocrine, and racial attributes, climatic differences and ingested substances such as salt. Identification of these possibilities is of utmost importance.

There are many theoretical reasons why cerebral and coronary beds are affected by atherosclerosis at different ages, but there have been few studies directed toward elucidation of causes. Among these could be mechanical factors related to movement of the arteries themselves, of the blood constituents within them, or differences in arterial blood pressure within the two vascular beds.

It is known that certain forms of heart disease increase the risk of cerebral infarction. While some of the mechanisms, such as emboli and the effects of reduced cardiac output, are well understood, others are not. Methods to protect the cerebral circulation of the individual with heart disease from secondary complications leading to cerebral infarction are needed.

The possible relationship between cerebral hemorrhage and transient elevations of blood pressure, as occur in emotional crises, is not known. The effects of sudden reduction in blood pressure as possible precipitants for cerebral infarction are not understood.

The use of certain oral contraceptive medications is accompanied by an increased risk of cerebral infarction in some women, particularly those with migraine. Whether this is related to accelerated atherosclerotic change in the arterial wall, to change in the blood constituents, or to the precipitation of hypertension or diabetes mellitus is unknown.

Bruits discovered in the cervicocranial arteries of asymptomatic individuals pose a particularly difficult problem. Such murmurs have many causes, ranging from inconsequential to the very serious. As a general rule, the older the person, the more likely a murmur in the chest, neck, or head is due to atherosclerosis. In this population the question that arises is whether the murmur is a predictor of future arterial occlusion or of thromboembolism to the brain. Informed opinion on this matter is divided. However, a consensus must be reached because as asymptomatic populations are screened, such murmurs will be found with increasing frequency and the proper management must be defined.

Recommendations

1. All persons, particularly young asymptomatic individuals, with blood pressure elevations should be identified and treated. In order to accomplish this goal, a program of national scope must be undertaken which should include education of the public and of health professionals to heightened awareness of the dangers of hypertension and to the necessity for its early recognition, accurate diagnosis, and vigorous management.

2. Screening techniques such as those discussed under the section on hypertension should be employed to detect individuals at increased risk of cerebral hemorrhage and infarction. In addition, screening for aorto-cervico-atherosclerotic cerebrovascular disease should be considered.

Techniques to consider include screening for murmurs in the neck, radioisotopic flow studies, thermography, and measurement of retinal arteriolar pressures.

3. Further investigations are needed to determine the degree of risk associated with individual as well as combinations of factors predisposing to cerebral infarction and hemorrhage.

4. Epidemiological investigations should be undertaken into the causes of variation in incidence and prevalence of stroke among races, sexes, and geographic regions in an effort to determine predictors of stroke and to gain new knowledge about prevention of stroke.

5. Studies of the relationship between various cardiac disorders as precipitants for stroke need to be initiated.

6. The undertaking of a controlled study to determine the natural history and the proper management of asymptomatic individuals with abnormalities of the aortocervicocranial arteries should be considered.

7. A systematic postmortem radiographic and anatomic investigation and analysis of the anatomical configuration of the entire aortocervicocranial arterial network needs to be done in order to determine if there are anatomical predictors for stroke which may be corrected.

8. Women on oral contraceptive medications should be examined carefully for risk factors which may be associated with an increased risk of cerebrovascular complications. There is a need to develop contraceptive techniques which will eliminate the increased risk of cerebral infarction which is

associated with the use of current pharmacological agents in certain population groups.

9. Further research is needed on the possible effects of transitory elevations or reductions in arterial blood pressure as precipitants for stroke.

References

1. Toole JF, Patel AN: Cerebrovascular Disorders. First edition. New York, McGraw-Hill Book Co, 1967, p 80

2. Fields WS: Surgery for occlusive cerebrovascular disease: Progress report of the joint study of extracranial arterial occlusion. Cerebral Vascular Diseases. Transactions of the Fifth Conference. Edited by CH Millikan, RG Siekert and JP Whisnant. New York, Grune & Stratton, 1966, pp 245-253

3. Wylie EJ, Ehrenfeld WK: Extracranial Occlusive Cerebrovascular Disease: Diagnosis and Management. First edition. Philadelphia, WB Saunders Co, 1970, p 231

4. Baker RN, Whisnant JP, Kuller L: Transient Ischemic Attacks. Transaction of the Seventh Princeton Conference on Cerebral Vascular Diseases. Edited by JF Toole, J. Moossy and R Janeway. New York, Grune & Stratton, 1970, pp 161-188

5. Fields WS, Maslenikov V, Meyer JS, et al: Joint study of extracranial arterial occlusion: V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. JAMA 211:1993-2003, 1970

6. Bauer RB, Meyer JS, Fields WS, et al: Joint study of extracranial arterial occlusion: III. Progress report of controlled study of long-term survival in patients with and without operation. JAMA 208:509-518, 1969

7. Blaisdell WF, Clauss RH, Galbraith G, et al: Joint study of extracranial arterial occlusion: IV. A review of surgical considerations. JAMA 209:1889-1895, 1969

8. Crawford ES, DeBakey ME, Morris GC Jr, et al: Surgical treatment of occlusion of the innominate, common carotid and subclavian arteries: A 10-year experience. Surgery 65:17-31, 1969

9. Siekert RG, Whisnant JP, Millikan CH: Surgical and anticoagulant therapy of occlusive cerebrovascular disease. Ann Intern Med 58:637-641, 1970

10. Levine J, Swanson PD: Diagnosis and treatment: Nonatherosclerotic causes of stroke. Ann Intern Med 70:807-816, 1969

11. Wylie CM: The community medicine of cerebrovascular disease. Stroke 1:385-396, 1970

12. Stallones RA: Epidemiology of cerebrovascular disease: A review. J Chronic Dis 18:859-872, 1965

13. Kannel WB, Dawber TR, Cohen ME, et al: Vascular disease of the brain--epidemiologic aspects: The Framingham Study. Amer J Public Health 55:1355-1366, 1965

14. Kurtzke JF, Kurland LT: Epidemiology of cerebrovascular disease. Cerebrovascular Survey Report for Joint Council Subcommittee on Cerebrovascular Disease, National Institute of Neurological Disease and Stroke, and National Heart and Lung Institute. Edited by RG Siekert. Rochester, Minn, Whiting Printers and Stationers, 1970, pp 163-175

15. Kurtzke JF: Epidemiology of Cerebrovascular Disease. Heidelberg, New York, Springer-Verlag, 1969

16. Cumings JN, Grundt IK, Holland JT, et al: Serum-lipids and cerebrovascular disease. Lancet 2:194-195, 1967

17. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213:1143-1152, 1970

18. Cole FM, Yates PO: Comparative incidence of cerebrovascular lesions in normotensive and hypertensive patients. Neurology 18:255-258, 1968

19. Kannel WB, Wolf PA, Verter J, et al: Epidemiologic assessment of the role of blood pressure in stroke: The Framingham Study. JAMA 214:301-310, 1970

20. Deming QB: Blood pressure: its relation to atherosclerotic disease of the coronaries. Bull NY Acad Med 44:968-984, 1968

21. Baker AB, Resch JA, Loewenson RB: Hypertension and cerebral atherosclerosis. Circulation 39:701-710, 1969

22. Kannel WB, Wolf PA, Verter J, et al: Epidemiologic assessment of the role of blood pressure in stroke. The Framingham Study. JAMA 214:301-310, 1970

23. The Council on Cerebrovascular Disease: Risk Factors in Stroke Due to Cerebral Infarction. A Statement for Physicians. American Heart Association, 1971

24. Kannel WB: Current status of the epidemiology of brain infarction associated with occlusive arterial disease. Stroke 2:295-318, 1971

25. Friedman GD, Loveland DB, Ehrlich SP: Relationship of stroke to other cardiovascular disease. Circulation 38:533-541, 1968

26. Gifford AJ: An epidemiological study of cerebrovascular disease. Amer J Public Health 56:452-461, 1966

27. Baker AB, Flora GC, Resch JA, et al: The geographic pathology of atherosclerosis: A review of the literature with some personal observations on cerebral atherosclerosis. J Chronic Dis 20:685-706, 1967

28. Williams AO, Resch JA, Loewenson RB: Cerebral atherosclerosis--a comparative autopsy study between Nigerian Negroes and American Negroes and Caucasians. Neurology 19:205-210, 1969

29. Kannel WB, Troy BL, McNamara PM: Epidemiology of Stroke. US Department of Health, Education and Welfare, Public Health Service, National Institutes of Health. Washington, D. C. US Government Printing Office, PHS Publication No. 1607, 1967

30. United States Department of Health, Education, and Welfare, Public Health Service, Washington, D.C: Cerebrovascular Disease Epidemiology: A Workshop, Public Health Monograph No 76

31. World Health Organization: World Health Statistics Report, Vol 22, No 9, 1969

32. Baker AB, Katsuki S, Editors: A study of a Caucasian and Oriental population. Geriatrics 83-84, 1969

33. Katsuki S, Hirota Y: Current concept of the frequency of cerebral hemorrhage and cerebral infarction in Japan. Cerebral Vascular Diseases. New York, Grune & Stratton Inc, 1966, pp 99-111

34. The President's Commission on Heart Disease, Cancer and Stroke: A National Program to Conquer Heart Disease, Cancer and Stroke--Volume I. U.S. Government Printing Office, Washington, D. C., 1964

35. Borhani NO, Meyer JS, Editors: Medical Basis for Comprehensive Community Stroke Programs. Washington, D. C., National Institutes of Health, 1968

36. Masi AT, Dugdale M: Cerebrovascular diseases associated with the use of oral contraceptives: A review of the English-language literature. Ann Intern Med 72:111-121, 1970

37. Fletcher AP, Alkjaersig N: Cerebral infarction and oral contraceptive agents. Transactions of the Seventh Princeton Conference on Cerebral Vascular Diseases. Edited by J Toole, J Moossy and R Janeway. New York, Grune & Stratton, 1971, pp 188-194

38. Paffenbarger RS, Wing AL: Characteristics in youth predisposing to fatal stroke in later years. Lancet 1:753-754, 1967

39. Paffenbarger RS, Williams JL: Chronic disease in former college students. V. Early precursors of fatal stroke. Amer J Public Health 57:1290-1299, 1967

40. Paffenbarger RS, Laughlin ME, Gima AS, et al: Work activity of longshoremen as related to death from coronary heart disease and stroke. New Eng J Med 282:1109-1114, 1970

41. McDowell FW, Louis J, Monahan K: Seasonal variation of non-embolic cerebral infarction. J Chronic Dis 23:29-32, 1970

C. PERIPHERAL

Current State of Knowledge

Atherosclerosis of the peripheral arteries affects the function of many organs and tissues, primarily the extremities. Veins are involved less generally with atheroma formation, but in the presence of venous hypertension (as in portal hypertension) atheroma can form in the affected veins.

Atherosclerosis does not uniformly affect the entire anatomic extent of a vessel. The involvement is "segmental" or discontinuous, and this fact permits the several reconstructive procedures now employed in peripheral vascular surgery. In some situations, arteries may be involved only at their origins, as in Takayasu's disease where branches of the arch of the aorta are involved for only a short extent distal to their origin from the aortic arch. The distal aorta may be involved to the point of complete occlusion, but the process usually extends proximally for only a short distance above its bifurcation. Interestingly, the development of an obstructing lesion in an artery may provide some protection against the development or progression of atheromatous changes distal to the lesion.

From the clinical standpoint, peripheral atherosclerosis causes either obstruction of the lumen or weakening of the arterial wall resulting in aneurysm. The suggestion has been made that these represent two entirely different processes. It can be argued whether the types are etiologically different, but certainly their natural history is different.

1. The obstructive form. This form of atherosclerosis seldom causes complete occlusion of the aorta except at or near its bifurcation. The

branches of the aorta, on the other hand, are commonly involved and often become completely occluded. This occurs in vessels as large as the innominate, subclavian, renal, splanchnic, and iliac, as well as smaller vessels.

2. The anuerysmal form. The atherosclerotic process in the aorta and its largest branches may result in aneurysmal dilation. Aneurysms of arteries smaller than the common carotids, the brachials, and the popliteals are rare. Aneurysms in arteries the size of the dorsalis pedis or radial and ulnar do occur, but are likely to be post-traumatic, syphilitic or congenital. If the atherosclerotic process leading to aneurysms differs from that leading to obstruction of the vessel lumen, it is reasonable to inquire into the nature of the difference. No evidence is available to suggest that the process involves different elements of the vessel wall. If the media and elastica were involved in the aneurysmal form, and the intima in the obstructive form, the development of aneurysm in the one and obstruction in the other would be understandable. Evidence for such selective involvement is not available.

Since aneurysms develop in vessels of large diameter, it is possible that in the large arteries and in the aorta itself the intraluminal pressure has a greater stretching effect than upon the walls of the smaller vessels. According to the LaPlace relationship, the tension in the arterial wall is a function of both the pressure and the radius of curvature. In general, once developed, an aneurysm can only increase in size and eventually rupture, since the wall tension (stress) will be further increased by a given intraluminal pressure as the radii of the curvature of the aneurysmal dilatation of the artery increase and its wall becomes thinner (stress = tension/wall thickness). Regardless of possible differences in pathogenesis, the clinical implications of obstructive disease and aneurysm are different. Obstructive atherosclerosis in the peripheral arteries carries a high morbidity while aneurysm carries a high mortality.

Peripheral Atherosclerosis and Diabetes. A relationship between diabetes mellitus and atherosclerosis is generally recognized. Diabetic patients develop atherosclerosis earlier than non-diabetic individuals, and the condition is likely to be more extensive and to involve smaller vessels. Atherosclerosis is more common and more severe in men than women in non-diabetics. In the presence of diabetes atherosclerosis is equally prevalent and severe in both sexes.

Other aspects of diabetes mellitus apart from its relation to carbohydrate metabolism are associated with vascular disease. Anatomic vascular changes have been noted in the microcirculation, i.e., venular micro-aneurysms. Of particular interest is the genetic concept that cellular longevity is decreased among diabetics so that the rate of cellular replacement is increased.

The replacement of an "old" fibroblast by a "young" one with increased frequency may be associated with an increased accumulation of collagenous matrix and atherosclerosis.

Other changes among diabetics are important in terms of the morbidity of their disease. The common development of peripheral neuropathy allows the patient to inflict trauma to the extremities in the absence or near absence of pain. The microcirculation loses its capacity for autoregulation and behaves as if denervated. These vascular characteristics of patients with diabetes are important in terms of morbidity and mortality from atherosclerosis.

Distribution of Lesions. Obstructing atheromatous of lesions are common in arteries as large as those arising from the arch of the aorta and its bifurcation. Lesions occur fairly frequently at the bifurcation of the aorta and occasionally involve nearly the entire abdominal aorta extending above the level of the renal arteries. The arteries commonly and significantly affected by obliterative atheromas are arteries smaller than the primary branches of the aorta. However, the internal carotid and vertebral arteries are frequently involved and even more commonly the lower segments of the femoral arteries, the popliteal arteries, and their distal branches.

Aneurysms secondary to atherosclerosis occur in the aorta and its large primary branches, i.e. the ascending and transverse limbs of the arch of the aorta, the entire descending aorta, the iliac and upper femoral arteries, and the popliteal artieries. Below this level, atherosclerotic aneurysms are very rare. They are less common in arteries which supply the upper extremities than in those which supply the lower extremities. Blood contained within aneurysms forms layers of clots against the wall of the aneurysm. Rarely, in patients with small aneurysms, this process may develop to the point of complete occlusion. Complete obliteration of aneurysms seldom occurs in the large arteries including the aorta. Occlusion of distal arteries may occur when pieces of thrombus contained within aneurysms break off and become lodged at distal bifurcations, or when the deposition of lamellae of thrombus progresses to the point of encroaching upon the ostia of tributary arteries.

Clinical Stages of Peripheral Atherosclerosis. Obstructive arterial disease may pass unnoticed if it affects the flow of blood through arteries which supply tissues and parts of organs not essential to biologic processes. Thus minor infarctions of parts of the kidneys, the spleen, brain, and of the heart itself may develop without causing symptoms. Large infarctions which affect organs or parts of organs which serve a vital irreplaceable function, however, are easily recognized. Such infarctions may result in disability or death.

Obstructive disease of the arteries can interfere with blood flow to an extent insufficient to cause infarction, but sufficient to prevent the increases in flow demanded by work or activity beyond the basal level. Intermittent claudication, and "intestinal angina" are examples of the consequences.

Finally, obstructive disease of the arteries may be severe enough to result in reduced circulation under basal conditions or at rest, but not severe enough to cause infarction. Rest pain in the extremities, usually involving the toes and part of the foot, is an example of this degree of obliterative disease.

Preclinical Atherosclerosis. Atherosclerosis of the peripheral arteries is a widespread condition affecting people of all nations. Its prevalence among peoples in different parts of the world is known to vary, but the prevalence in any specific group is not known because the condition remains occult for many years, in many cases for a lifetime. Atherosclerosis is only rarely found in infants and children; beyond the age of 40, however, the lesions are commonplace.

Some idea of the prevalence of asymptomatic, but clinically detectable, atherosclerosis can be obtained from a study of 6,400 employees in pharmaceutical companies.[1] As many as 7 percent of male employees were found to have clinically demonstrable peripheral arterial occlusion. Only one third of them had symptoms referrable to the lesions.

The degree to which arteries which supply different organs in the same individual develop atherosclerosis varies, and the rate of progression varies for different organs. Lesions progress more rapidly in diabetics than in non-diabetics and more rapidly in men than in women. A clinical impression suggests that certain individuals will have predominant involvement of arteries in one or another of the vital organs, i.e., the brain, the heart, and the kidneys. These vascular beds are seldom involved to the same extent, However, some 16 percent or more of patients with peripheral arterial disease also have symptomatic involvement of the coronary arterial circulation.[2] Similarly, patients with symptomatic coronary arterial disease often will have evidence of peripheral arterial disease, albeit asymptomatic.[3]

Unresolved Problems

In addition to unresolved questions pertinent to the whole area of atherosclerosis detailed in the sections on The Lesion and on Thrombosis, certain specific problems in presymptomatic peripheral atherosclerosis may be singled out as examples of issues needing clarification.

One area that needs clarification is the physiology and pharmacology of the peripheral circulation in diabetes. Surprisingly little information is available concerning the responsiveness to humoral and neural stimuli of blood vessels in diabetic subjects and in animals with experimental diabetes.

Responsiveness here refers not only to the contraction of smooth muscle but to changes in the properties of arterial non-muscular tissue as well.

The pathologic characteristics which determine the progression of a peripheral lesion to obstructive disease on the one hand or to aneurysmal disease on the other, are not yet identifiable.

The actual prevalence of asymptomatic peripheral atherosclerosis is not known especially among the young. In particular, the rate of progression is unknown.

Noninvasive techniques are needed to assess the extent of peripheral atherosclerosis. Some progress in this area has already been made employing ultrasound through the Doppler and echo effects. Additional approaches, employing resonance, laser beam, and other techniques, need to be explored and developed with the prospect of identifying plaques within arteries and of documenting their rate of growth or progression. Further refinements need to be made in techniques already available.

RECOMMENDATIONS

1. *The epidemiology of presymptomatic peripheral arteriosclerosis, including prevalence and natural history, should be investigated.*

2. *Instrumentation must be further developed for noninvasive study of blood vessels in man to obtain data concerned with prevalence and progression of atherosclerosis including peripheral atherosclerosis.*

3. *In addition to research on the heart and other viscera, emphasis should be placed on studies of the peripheral vessels because they are more readily*

accessible than visceral, cardiac, and cerebral arteries and thus provide a useful way to follow changes in atherosclerotic lesions over a period of time.

4. Facilities need to be developed wherein, along with basic research, samples of populations can be studied so as to obtain information on prevalence and rate of growth of the lesions in presymptomatic peripheral atherosclerotic disease.

References

1. Widmer LK: Periphere Atherosklerose: Ihre frühzeitige Erfassung und Bedeutung in der Praxis. Schweiz Med Wschr 93:1583-1591, 1963
2. Juergens JL, Barker NW, Hines EA: Arteriosclerosis obliterans: Review of 520 cases with special references to pathogenic and prognostic factors. Circulation 21:188-195, 1960
3. McDonald L: Ischaemic heart disease and peripheral occlusive arterial disease. Brit Heart J 15:101-107, 1953

D. PULMONARY

Current State of Knowledge

Pulmonary arteriosclerosis of the *large* pulmonary arteries is common beyond age 40. Its occurrence is facilitated by pulmonary arterial hypertension. However, per se, it is *not* clinically manifest.

Arteriosclerosis of the small pulmonary arteries is generally associated with severe pulmonary hypertension and unless this hypertension either strains the right heart or produces angina-like pain, it has no clinical significance. Although pulmonary hypertension is of great clinical interest, in that it may not only determine the natural history of certain types of acquired and congenital heart disease but also the prognosis after surgery, study of this form of arteriosclerosis is not apt to bear directly on the usual types of large vessel arteriosclerosis that are encountered in the systemic circulation.

Unresolved Problems

With respect to the pathogenesis of arteriosclerosis, the pulmonary circulation provides an unusual natural setting since it operates at a low blood pressure and is perfused by hypoxemic blood. Unfortunately, opportunities for systematic study of the genesis of pulmonary arteriosclerotic lesions in man are slim because of the paucity of clinical material for study and the inability to define the temporal sequence of anatomic changes in the random opportunities that do occur.

Recommendations

1. Particular attention should be paid to the pathogenesis of pulmonary arteriosclerosis, in both large and small vessels, because of the unusual setting of low pressure and hypoxemia. In addition, attempts should be made to dissociate the influences of pressure, flow, viscosity, and local thrombosis in generating the arteriosclerotic lesions and in determining localization in the smaller pulmonary arteries. Not only the segment of the vessel affected, but also the reactions of intimal and medial layers should be studied. The etiologic role of organized thrombo-emboli in the pathogenetic sequence of pulmonary arteriosclerosis of small vessels should be investigated.

2. Since clinical opportunities to settle these problems will undoubtedly remain scarce, the development of animal models for generating replicas of clinical pulmonary arteriosclerosis should be encouraged. These studies should make provision for analysis of the regression of the lesions as well as their evolution.

References

1. Liebow AA: Arteriosclerosis of the pulmonary circulation. Cowdry's Arteriosclerosis: A Survey of the Problem. Second Edition. Edited by HT Blumenthal. Springfield, Ill, Charles C Thomas, 1967, pp 248-328

2. Saldana ME, Harley RA, Liebow AA, et al: Experimental extreme pulmonary hypertension and vascular disease in relation to polycythemia. Amer J Path 52:935-981, 1968

3. Naeye RL, Vennart GP: The structure and significance of pulmonary plexiform structures. Amer J Path 36:593-605, 1960

4. Edwards JE: The Lewis A. Conner Memorial Lecture: Functional pathology of the pulmonary vascular tree in congenital cardiac disease. Circulation 15:164-196, 1957

5. Heath D, Brewer D, Hicken P: Cor Pulmonale in Emphysema: Mechanisms and Pathology. Edited by IN Kugelmass. Springfield, Ill, Charles C Thomas, 1968, p 114

V. OVERT ATHEROSCLEROTIC DISEASE

A. CORONARY

1. Angina Pectoris

Current State of Knowledge

Angina Pectoris is a clinical syndrome which is characterized by distinctive chest pain or sensation of pressure, often radiating to the upper extremity, neck or jaws, and precipitated by walking, other exertion, or emotion. The pain is usually relieved within a few minutes by rest or nitroglycerin taken sublingually.

The mechanism responsible for this chest discomfort is an inadequate blood supply to the myocardium with respect to its oxygen needs at a given time. Occasionally angina pectoris is due to aortic valvular disease but in the large majority of cases it is associated with advanced occlusions of the coronary arteries produced by atherosclerosis. Such occlusions may be demonstrated by coronary angiography.

Depending on the degree of occlusion and the adequacy of collateral circulation, angina pectoris due to coronary atherosclerosis may or may not be associated with myocardial infarction. If there is no infarction or extensive scarring, the electrocardiogram may be normal while the patient is at rest. However, during imposed stress such as exercise, artificial acceleration of the heart by way of a pacemaker in the right atrium, or by means of pharmacologic agents which increase the work of the heart, the inadequacy of coronary blood flow may be exposed and characteristic changes in the electrocardiogram, notably depression of the ST segment, become apparent.

Angina pectoris usually runs a long course during which symptoms occur intermittently with certain stresses and subside rapidly, and there is relatively little disability. This is termed stable angina. From time to time angina pectoris becomes intensified (unstable) either because of severe or persistent stress, progression in the severity of the occlusive process, or a new coronary occlusion. An unexplained increase in severity or frequency of anginal discomfort, especially if unresponsive to nitroglycerin, often indicates impending or actual acute myocardial infarction. Eventually most patients with angina pectoris experience one or more myocardial infarctions. Sudden death is a frequent form of demise irrespective of the development of acute or healed myocardial infarction.

In general the long-term prognosis of patients with angina pectoris is worse in the presence of coexisting hypertension, congestive failure or cardiac enlargement. Recently, prognosis has been shown to correlate well with the severity of the atherosclerotic narrowing of the coronary arteries displayed by angiography.

Medical treatment is generally directed toward relieving symptoms and is often unsatisfactory. Consequently, many surgical procedures have been tried in the attempt to relieve or eliminate angina pectoris by increasing the blood flow to the potentially ischemic portion of the myocardium. Until recently surgical intervention was of dubious value; currently, operations are in vogue which create a shunt from the aorta to the coronary artery using a section of vein from elsewhere in the body, thereby detouring blood flow to the heart past the site of obstruction. This by-pass procedure holds more promise of symptomatic relief than any previous procedure even though its full value and precise role in the management of angina pectoris still remain to be clarified.

Unresolved Problems

Myocardial ischemia is the probable cause of angina pectoris. However, the precise mechanism responsible for the chest pain or pressure, the reasons for the variability of the clinical syndrome in different patients and even in the same patient at different times, and the mechanisms responsible for angina pectoris which occurs without apparent occlusive disease of the coronary arteries, and without other explanation are unresolved problems.

There is no satisfactory noninvasive method for determining myocardial blood flow and its regional distribution. Since the diagnosis of angina pectoris implies an abnormality of the coronary blood flow, lack of such methods impairs the reliability of diagnosis. At present the physician depends upon indirect indices in order to determine the adequacy of the coronary circulation; these include the patient's symptoms and the electrocardiogram at rest and during exercise. These indices are neither very sensitive nor highly specific. Although improvements in the technical aspects of "stress electrocardiography" continue to be developed, such indirect tests have inherent limitations for the assessment of the adequacy of the coronary circulation. Disagreement persists concerning the indications for coronary angiography because of some morbidity, occasional mortality, and considerable expense.

Methods for identifying those patients with angina pectoris who are at highest risk of acute myocardial infarction or sudden death are sorely needed since the proper application of pharmacologic agents, surgical procedures, or other therapeutic measures may help to delay, or to prevent, these complications. The merits and indications for the use of long-acting nitrates and beta-adrenergic blocking agents in angina pectoris[1,2] are also unresolved. Better anti-anginal drugs than those currently available are urgently needed.

The role of coronary artery bypass surgery in patients with angina pectoris is still undetermined. The widespread acceptance of the operation makes it difficult to perform a randomized, controlled study. On the other hand, there are enormous gaps in our knowledge of the natural history of angina pectoris and especially in our capacity to predict the natural course in individual patients. Without such knowledge, it is extremely difficult to assess the benefits of coronary surgery with respect to the patient's development of coronary complications, longevity, and even with respect to the alleviation of anginal pain. The long-term results of the operation with respect to patency of the venous graft, run-off of coronary flow beyond the graft, and late complications or mortality, are as yet unknown.

Still unclear is the degree of correlation among the coronary angiographic findings, the clinical manifestations, and the electrocardiographic findings with stress tests. Also, the role of exercise and the definition of suitable types of exercise, still has to be established for patients with angina pectoris.

Recommendations

1. Noninvasive techniques should be improved or developed for the early detection, precise diagnosis, and serial studies of coronary atherosclerosis in patients with angina pectoris.

2. The natural history of angina pectoris as a basis for evaluating therapeutic interventions should be studied.

3. More effective drugs for the control of angina pectoris should be developed.

4. Objective evaluation and standardization of exercise programs for the treatment of patients with angina pectoris is recommended.

5. The surgical treatment of angina pectoris by coronary bypass should be critically assessed and its place in managing angina pectoris should be defined.

2. Myocardial Infarction

Current State of Knowledge

It is generally believed that myocardial infarction is a consequence of acute occlusion of a coronary artery by formation of a thrombus on an atherosclerotic plaque with subsequent necrosis of myocardium if the collateral circulation is inadequate. On the other hand, some pathologists believe that myocardial infarction usually occurs without antecedant coronary thrombosis. This infarction without thrombosis is most likely to occur in patients with chronic angina pectoris or in persons without previous clinical manifestations of coronary arteriosclerosis. Nonetheless, both groups usually experience premonitory chest pressure or pain within a few hours or days preceding the actual infarct. In those with chronic angina pectoris the outstanding feature is a change in the pattern of the pain or discomfort: these premonitory symptoms persist longer, occur more frequently and with less provocation, or even without apparent cause (Figures 1 and 2).

When acute myocardial infarction does occur, it is generally diagnosed on the basis of chest pain or pressure which is usually of greater severity than that of angina pectoris and persists longer, often for several hours, until it subsides spontaneously or is relieved by opiates. The diagnosis is confirmed by electrocardiographic changes (pathologic Q waves, RST segment elevations and T wave inversions) with progressive alterations in serial electrocardiograms. When the infarct does not extend from endocardium to epicardium (transmural) but is limited to the subendocardial area or is patchy and intramural, there may be no abnormal Q waves, and only non-specific changes may be seen. Both in transmural and non-transmural myocardial infarction the diagnosis is also confirmed by increased concentrations in the serum of specific enzymes released by the infarcted heart muscle. Since the coronary thrombosis and myocardial infarction may evolve over a period of several days, fully diagnostic electrocardiographic and enzyme changes may not become apparent until several days after the onset of the acute attack.

The danger of a fatal outcome of acute myocardial infarction is related to pump failure (cardiogenic shock, acute pulmonary edema) arrhythmias (most often ventricular fibrillation), cardiac standstill or rupture of the heart. Pulmonary embolism, pericarditis, congestive heart failure, rupture of the

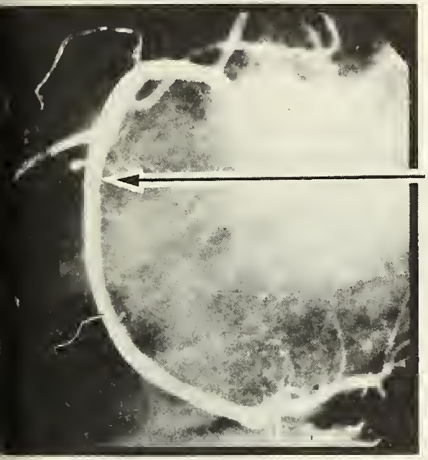
FIGURE 1

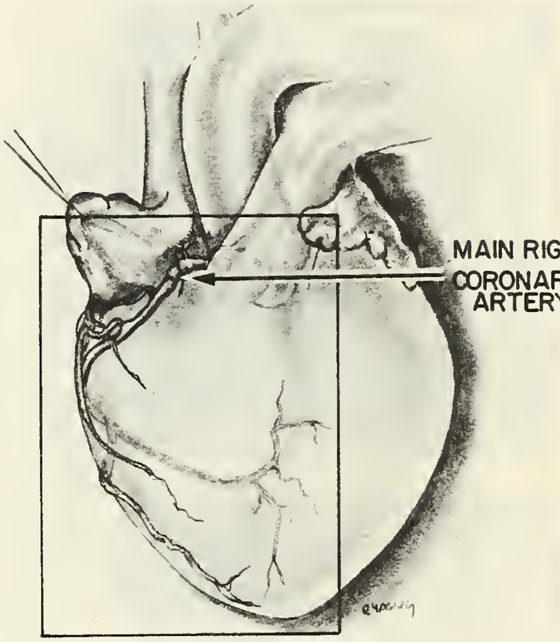
RIGHT CORONARY ARTERY

ORONARY ARTERIOGRAMS

IGHT CORONARY ARTERY

EFT ANTERIOR OBLIQUE PROJECTION





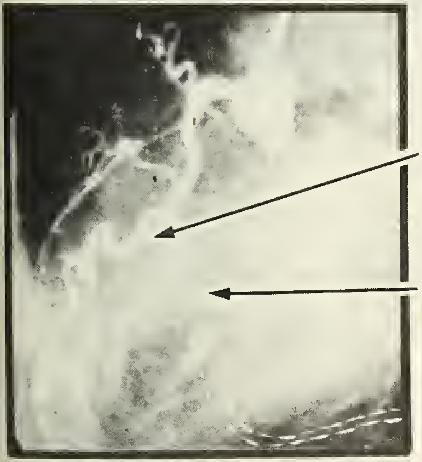
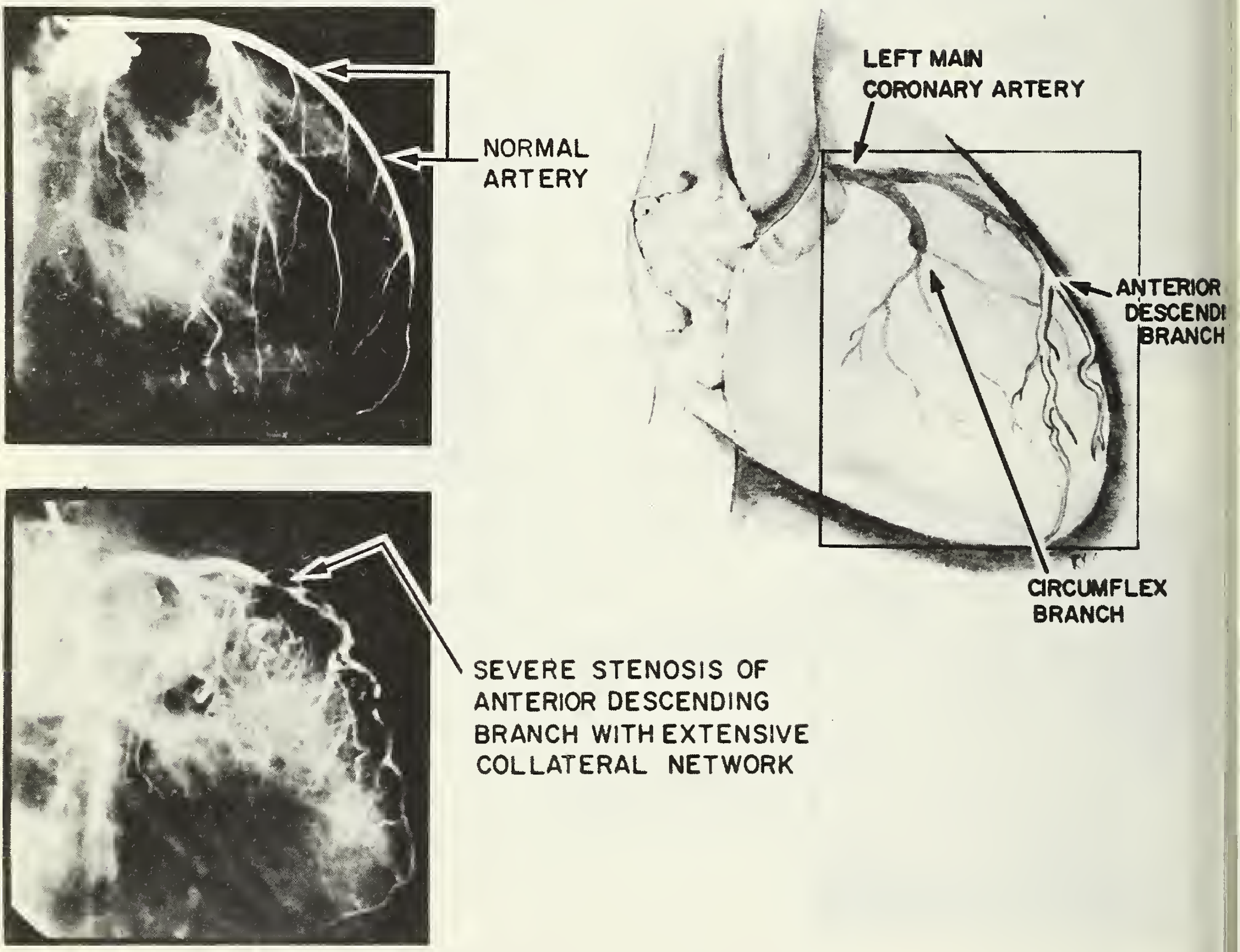


FIGURE 2

LEFT CORONARY ARTERY

CORONARY ARTERIOGRAMS

LEFT CORONARY ARTERY
RIGHT ANTERIOR OBLIQUE PROJECTION


NORMAL ARTERY
SEVERE STENOSIS OF ANTERIOR DESCENDING BRANCH WITH EXTENSIVE COLLATERAL NETWORK
LEFT MAIN CORONARY ARTERY
ANTERIOR DESCENDI BRANCH
CIRCUMFLEX BRANCH

interventricular septum or papillary muscle are other important complications.

Approximately 50 percent of all deaths from acute myocardial infarction occurs in the first two hours of the attack, before the patient can gain access to the monitoring and treatment that can be provided by a coronary care unit.[3] Death is usually due to a serious arrhythmia which may often be prevented or eliminated if appropriate treatment can be instituted promptly. Most patients in an urban coronary care unit arrive more than three hours following onset of their chest pain and the mean delay is 7 to 8 hours.[4] This delay is due chiefly to: patient procrastination in calling a physician either because of ignorance of the diagnostic significance and seriousness of symptoms or because of psychological reasons (denial of symptoms, unwillingness to disturb a physician at night, fear of hospitalization, hope for early spontaneous subsidence of symptoms); physician's delay in responding or arranging immediate coronary care because of uncertainty as to diagnosis, difficulties in communication or logistics; delay in transportation to obtain coronary care; and delay within the emergency room or elsewhere in the hospital.

Next to sudden or early death from acute myocardial infarction cardiogenic shock is the major cause of death, the mortality ranging from 80-90 percent or higher depending on the criteria for shock.[5,6] The treatment for cardiogenic shock is usually unsatisfactory. Fluid replacement, the use of vasopressor drugs and drugs to stimulate the heart, the use of oxygen, and control of arrhythmias and electrolyte disturbances are the mainstays of medical treatment of cardiogenic shock but they are usually ineffective.

Consequently efforts are being made to treat cardiogenic shock by means of circulatory assist devices (chiefly by appropriately timed pumping of a balloon inserted into the descending aorta). On occasion shock has been treated by surgical insertion of a venous graft bypassing the coronary occlusion; this is a specialized procedure involving coronary angiography while the circulation is being assisted by aortic balloon pumping and the talents of an expert surgical-medical team.

The ventricular septum or papillary muscle may rupture if infarcted. This complication is usually easy to recognize. Although prompt surgical intervention may be life saving, delay in surgical treatment is desirable, if possible.

Early treatment of acute myocardial infarction in coronary care units is becoming widespread. In some areas emergency ambulances equipped as mobile coronary care units attempt to provide resuscitation and modern coronary care promptly, wherever the patient happens to be, in an effort to stabilize his condition until he can be brought to a hospital coronary care unit. Similar coronary care facilities are being established in "life support stations" or emergency areas in large industrial plants, office buildings, and stadiums. Coronary care treatment is especially concerned with the vigorous treatment of arrhythmias which predispose to or herald life-threatening arrhythmias (ventricular tachycardia and ventricular fibrillation). Drugs such as atropine for slow cardiac rates (bradyarrhythmias) and lidocaine for ventricular premature beats and arrhythmias with rapid rates (tachyarrhythmias) can be administered out of the hospital. Within the hospital more specialized approaches such as the transvenous insertion of pacemakers for heart block or very slow heart rates which do not accelerate after administering atropine, are important forms of therapy.

As a result of prompt and intensive treatment in coronary care units, the hospital mortality from acute myocardial infarction has been reduced appreciably, i.e. from about 30 percent to 15-20 percent, essentially by reducing deaths from arrhythmias.[7,8]

The value of anticoagulation therapy in acute myocardial infarction is the subject of continuing controversy. However, it is in common use on the premise that it reduces the incidence of thromboembolic complications and, perhaps, mortality. Its importance has diminished as patients are permitted greater freedom of movement in bed, are encouraged to sit on a chair or commode very early, and are ambulated much earlier than formerly. Also, the overall therapeutic importance of anticoagulant therapy has been greatly diminished as pulmonary embolism has become relatively unimportant as a cause of death in comparison with the other complications noted.

Unresolved Problems

Whether an acute myocardial infarct results from thrombosis of a coronary artery or whether the thrombus develops secondary to the infarct, is still being debated. If the latter is the case, the cause of the infarct is not clear.

A variety of influences have been considered to be etiologically related to acute myocardial infarction. Among these are dietary, metabolic, reflex, and hormonal factors and psychologic disturbances. However, proof of their relationship and assessment of their relative contributions, is not yet available. If this assessment could be made, the way would be opened to preventive cardiology. The diagnosis of angina that will culminate in myocardial infarction in hours to days ("preinfarction angina") is of critical importance because of the high mortality in the first few hours after the actual infarction. If such diagnosis could be made with a low incidence of false alarms it would be possible to admit the patient to a pre-coronary care area where immediate treatment could be instituted as soon as the infarct occurred or, hopefully, prophylactic measures could be developed to prevent the infarct.

Another important problem is presented by the delay on the part of the patient with acute myocardial infarction in gaining entry into a system of modern coronary care. The major problem consists of educating and influencing patients to seek prompt coronary care, but delays, once the patient decides to seek assistance, also need to be avoided.

There is uncertainty as to how often fatal arrhythmias in the first few hours are preceded by bradycardia or by ventricular premature beats and whether or how often control of these preceding arrhythmias would reduce sudden or early death.

In the coronary unit there is uncertainty as to the precise indications for the use of various drugs, the control of dosage, and sometimes the choice of drugs. There is a problem in treating certain arrhythmias which persist despite the use of the conventional drugs in the conventional dosage. The indications and value of pacemakers in acute myocardial infarction are still undetermined.

Cardiogenic shock still carries a grim prognosis and lacks a standardized therapeutic approach. Particularly unclear are the roles of circulatory assistance, the performance of coronary angiography, and of coronary surgery.

There is uncertainty as to the merit and indications for myocardial resection, infarctectomy, or coronary bypass, as treatments for acute myocardial infarction.

Another problem is that of rehabilitation. The indications for most important measures in and effectiveness of rehabilitation programs following acute myocardial infarction need to be resolved. The role of exercise needs to be determined for those who have suffered an acute myocardial infarct as well as for those with angina pectoris. Whether long-term anticoagulation should be administered and the duration of such treatment are questions still not fully answered.

Recommendations

1. *The National Heart and Lung Institute should examine the feasibility of an educational program designed to inform the lay public, physicians and allied health personnel, including nurses and personnel in hospital emergency rooms of the urgency of immediate treatment at the onset of chest pain or pressure suggesting myocardial infarction. The program should define simple, minimal criteria of probable acute myocardial infarction or of impending myocardial infarction.*

2. *Systems for facilitating early care of the patient should be developed.*

Such systems should provide for adequate communication and transportation, and for satellite life support stations in industrial plants, stadiums, large office buildings, and other locations where concentrations of susceptible persons may be expected.

3. The incidence and significance of bradycardia and ventricular arrhythmias in the first two or three hours of acute myocardial infarction should be determined. If it appears desirable an evaluation should be made as to the feasibility and effectiveness of self-injection of atropine for bradycardia and of lidocaine for ventricular arrhythmias as soon as acute myocardial infarction is suspected.

4. More systematic data should be obtained as to the nature, frequency and significance of prodromal symptoms of acute myocardial infarction, differentiation from similar symptoms which may be misleading, and the duration between the warning symptoms and the actual acute infarct. The prophylactic efficacy of rest, antiarrhythmic and other drugs administered during this interval should be evaluated.

5. There should be agreement upon a definition and criteria for cardiogenic shock in acute myocardial infarction which will result in uniformity in collection of data, prognostic indices, and evaluation of therapeutic measures.

6. Consideration should be given to the advisability of a national registry of persons with coronary heart disease.

7. There needs to be investigation of methods for determining the size of

myocardial infarcts as a basis for categorizing cases, correlating size of infarct with occurrence of shock, estimating prognosis and evaluating therapy.

8. The study of noninvasive techniques for measuring regional myocardial blood flow in acute myocardial infarction should be supported.

9. The prognosis of the various subgroups of patients with acute myocardial infarction (classified according to clinical, hemodynamic and metabolic variables) requires further definition. Current efforts toward this goal by the Myocardial Infarction Branch deserve continued support.

10. Uniform criteria should be set for cardiogenic shock as a prerequisite for evaluating treatment. Balloon pumping and other circulatory assistance must be evaluated. From the various parameters noted above efforts should be made to identify early the patients who are likely to require circulatory assistance since effectiveness may depend on early intervention.

11. It is important to continue support of programs for development of animal models for acute myocardial infarction, aimed at improved understanding of its electrophysiological and hemodynamic consequences and their treatment.

12. A study is needed of methods to prevent extension of initial myocardial infarction by reducing oxygen consumption, e.g. by drugs and promoting blood supply. The usefulness and indications for performing coronary angiography and coronary bypass for pre-infarction angina should be evaluated.

13. Coronary care units or coronary care beds should be provided or increased where they are not now available or are inadequate. The effectiveness of coronary care units should be repeatedly evaluated and upgraded when necessary.

3. Sudden Death

Current State of Knowledge

Sudden death refers to natural death occurring unexpectedly within 24 hours of the onset of acute symptoms and signs. It is regarded as unexpected in that the victim was not confined to home or hospital and appeared to be able to conduct a relatively normal life. When sudden death is due to coronary atherosclerosis it usually occurs almost instantaneously or within an hour of the onset of acute symptoms or signs.

The mechanism of coronary sudden death is often unknown but in many patients studied at the time of occurrence, it appears to have been due to or associated with ventricular fibrillation. Less often it is due to cardiac standstill. The almost instantaneous occurrence of sudden death in other patients who are observed but not monitored at the time of the event also suggests that death results from an arrhythmia producing cardiac arrest.

Sudden death is responsible for about 60 percent of the fatalities from coronary arteriosclerotic heart disease.[9] In 50-65 percent of persons dying suddenly there is a previous history or symptoms of coronary heart disease and approximately 20 percent of those who died suddenly had consulted a physician during the previous week.[9,10] Statistics on sudden death are inadequate and unsatisfactory.

Sudden death in persons with coronary atherosclerosis may occur 1) during the preclinical stage, i.e., in previously asymptomatic persons; 2) in patients with stable or unstable angina during the course of pain or in its absence; 3) in patients with previous myocardial infarction with or without post-infarction angina; and 4) in the course of acute myocardial infarction especially in the first three hours.

The pathology of sudden death is uncertain. In medical examiners' cases of sudden death, coronary atherosclerosis with severe stenosis is more common than fresh coronary thrombosis or acute myocardial infarction. In several series of cases of sudden cardiac death there was a history of previous myocardial infarction in 30 percent.

Efforts have been made to identify asymptomatic persons likely to experience sudden death. The identifiable factors which have been implicated include cardiac enlargement, bundle branch block or heart block observed after the onset of myocardial infarction, the presence of ventricular premature beats especially in association with left ventricular hypertrophy or electrocardiographic evidence of myocardial damage, prolonged Q-T interval in the electrocardiogram, abnormal electrocardiographic response to stress tests, and history of cardiac syncope. It is known that the great majority of persons dying suddenly from coronary disease have been characterized by at least one of the major risk factors, i.e., hypertension, hypercholesterolemia, or a history of cigarette smoking.

Unresolved Problems

There are inadequate and unreliable data as to the incidence and circumstance of occurrence and other features in the epidemiology of sudden death.

It is uncertain whether the mechanism of sudden death is always ventricular fibrillation or cardiac standstill. In addition there is lack of knowledge as to their relative frequency and the circumstances under which one or the other is operative.

The basic electrophysiology including the precise mechanism which initiates fatal arrhythmias is uncertain or unknown.

The mechanism responsible for sudden death in preclinical coronary arteriosclerosis and in the absence of coronary thrombosis or myocardial infarction is unknown. It is not possible to predict accurately the individuals who will die suddenly or especially to predict those who will die suddenly within a brief period of time.

The premonitory manifestations of sudden death, if such exist except in those with preinfarction angina or early myocardial infarction, are unknown.

The histopathology of sudden death is unknown and it is not possible to determine from pathologic examination that a person died suddenly. The relation of sudden death to lesions in the conduction system, congenital or acquired, or to disturbance in the blood supply of the sinus or atrioventricular nodes has not been established.

We are unable to consistently prevent recurrent arrhythmias which may lead to sudden death by available drugs or other therapeutic modalities in presumably susceptible persons such as those with healed myocardial infarction or angina pectoris.

Recommendations

1. A uniform definition of sudden death should be formulated and a uniform protocol should be followed for gathering data as to the characteristics of persons who die suddenly, possible risk factors and warning symptoms.

2. Pathologic studies should be undertaken with new histochemical or other techniques to discover early cellular changes which might serve as the pathologic basis of sudden death and explain its mechanism.

3. Pathophysiologic (electrophysiologic) studies should be made to elucidate the mechanisms of arrhythmias and their relation to sudden death with special reference to the occurrence of ventricular fibrillation and standstill. The relation of hypoxia, changes in pH and electrolytes and of other possible factors to the development of these fatal arrhythmias should be investigated. Animal models to permit the induction of various arrhythmias by multiple techniques need to be developed.

4. Pharmacologic investigations should be fostered to produce new antiarrhythmic drugs and test their efficacy. Animal models should be developed to test these drugs and simulate the arrhythmias associated with myocardial ischemia and infarction rather than arrhythmias caused by digitalis, epinephrine or autonomic stimuli. The efficacy of currently available drugs in the long-term prevention of arrhythmias and sudden death should be assessed.

5. A registry of high risk persons should be developed to identify likely

candidates for sudden death not only with respect to expediting treatment but also to collect information which could lead to improved methods of diagnosis and to improve our understanding of the natural history of the disease.

4. Congestive Heart Failure

Current State of Knowledge

Congestive heart failure may occur in patients with coronary atherosclerotic heart disease either during acute myocardial infarction or after the myocardial infarct has healed. In acute myocardial infarction it is a manifestation of pump failure and may be associated with cardiogenic shock or not. Minor degrees of left heart failure may be apparent as interstitial pulmonary edema, basilar pulmonary rales, dyspnea, orthopnea at rest, or there may be frank clinical pulmonary (alveolar) edema. Severe degrees of heart failure are associated with high rates of mortality, exceeding 40 percent. If shock is also present the mortality is 80 percent or more.[5] Mild or moderate degrees of heart failure subside as the infarct heals, or with therapy including use of digitalis and diuretics, control of arrhythmias, and restriction of sodium and fluid intake.

Severe acute left, or left and right heart failure, may occur during the course of the acute infarct as a result of rupture of a papillary muscle or rupture of the interventricular septum. When acute heart failure results from these complications, medical treatment is undertaken and may permit delaying surgery until a more favorable time. Heart failure may also be precipitated by an arrhythmia or pulmonary embolism for which appropriate treatment is instituted and is often effective.

When congestive heart failure becomes manifest after healing of the infarct, it is generally the result of a complicating ventricular aneurysm, mitral regurgitation due to dysfunction of the papillary muscle, or to extensive akinetic or dyskinetic areas of myocardium representing healed (scarred) areas of myocardial necrosis. In general, heart failure due to coronary atherosclerotic heart disease in a patient without acute myocardial infarction is due not to myocardial ischemia alone but to the consequences of preceding myocardial infarction. These consequences include rupture of the interventricular septum or of a papillary muscle, papillary muscle dysfunction producing mitral regurgitation, ventricular aneurysm, or extensive scarring. However, occasionally heart failure is present in a patient with angina pectoris, an abnormal electrocardiogram and cardiac enlargement but without a history of myocardial infarction and without specific evidence of healed myocardial infarction in the electrocardiogram. Nevertheless, based upon subsequent autopsy, the underlying pathology is healed myocardial infarction with scarring, with or without aneurysm or other complications noted above.

Unresolved Problems

Although heart failure in acute myocardial infarction is due to myocardial damage, there is uncertainty as to the relative importance of the extent and location of damage and any other factors which determine the development of congestive heart failure or shock.

When there is a rupture of the interventricular septum or a papillary muscle, there is often uncertainty as to whether surgical correction should be undertaken promptly or whether it can be delayed until after the infarct has healed. Immediate surgery carries a very high mortality rate, while medical treatment is unsuccessful in most but not all patients.

When heart failure develops after healing of myocardial infarction, there is uncertainty as to whether revascularization by a coronary bypass operation can restore ischemic myocardial fibers or otherwise promote myocardial function and thus alleviate heart failure. There is preliminary information suggesting that in patients with disease of multiple coronary vessels and very large hearts, revascularization procedures are associated with high mortality and generally unsatisfactory results in the survivors.[11]

The indications for surgery to excise a ventricular aneurysm are not clearly defined. The value of excision of myocardial scars in the treatment of heart failure, the amount of tissue that should be excised, and the possible danger of excising functioning myocardial fibers, are unresolved problems.

Recommendations

1. Research should be carried out to determine the mechanism responsible for the presence or absence of heart failure and its relation to cardiogenic shock.

2. Pathologic studies should be made to correlate the extent and location of myocardial infarction and scars of healed infarcts with the development of heart failure.

3. The value of surgical techniques for excision of ventricular aneurysm, repair of ruptured septum or papillary muscle, resection of scars and areas of dyskinesis, and for myocardial revascularization by a bypass graft or *other means should be evaluated systematically in the treatment of heart failure due to coronary atherosclerosis, with particular reference to indications, contraindications, value, and risks.*

References

1. Weisse AB, Regan TJ: The current status of nitrites in the treatment of coronary artery disease. Progr Cardiovasc Dis 12:72-82, 1969

2. Elliott WC, Stone JM: Beta-adrenergic blocking agents for the treatment of angina pectoris. Progr Cardiovasc Dis 12:83-98, 1969

3. Fulton M, Julian DG, Oliver MF: Sudden death and myocardial infarction. Circulation 39,40:Suppl 4:182-193, 1969

4. McDonald L: The London Hospital. Acute Myocardial Infarction. Edited by DG Julian, MF Oliver. Baltimore, Williams & Wilkins Co, 1969, p 29-36

5. Lown B, Vassaux C, Hood WB Jr, et al: Unresolved problems in coronary care. Amer J Cardiol 20:494-507, 1967

6. Page DL, Caulfield JB, Kastor JA, et al: Myocardial changes associated with cardiogenic shock. New Eng J Med 285:133-137, 1971

7. Lown B, Fakhro AM, Hood WB, et al: The coronary care unit: New perspectives and directions. JAMA 199:188-198, 1967

8. Killip T, Kimball JT: A survey of the coronary care unit: Concept and results. Progr Cardiovasc Dis 11:45-52, 1968

9. Kuller L, Lilienfeld A, Fisher R: Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. Circulation 34:1056-1068, 1966

10. Wikland B: Death from arteriosclerotic heart disease outside hospitals: A study of 2678 cases in Stockholm with particular reference to sudden deaths. Acta Med Scand 184:129-133, 1968

11. Kouchoukos NT, Doty DB, Buettner LE, et al: Treatment of postinfarction cardiac failure by myocardial excision and revascularization. Circulation 43,44:Suppl II:108, 1971

B. CEREBRAL

Current State of Knowledge

Stroke syndromes are caused by several basic pathologic processes. One is the focal reduction in arterial flow and pressure due to atherosclerosis resulting in loss of tissue perfusion.[1] If ischemia is sufficiently prolonged, tissue death results. Cerebral infarction is a manifestation of end-stage atherosclerosis and is the result of one or more pathophysiologic processes such as atherothrombosis, microembolism, or hypotension which overcome the ability of the arteries supplying the brain to provide it with oxygenated, glucose-containing blood in adequate volume under appropriate pressures (Figure 1).

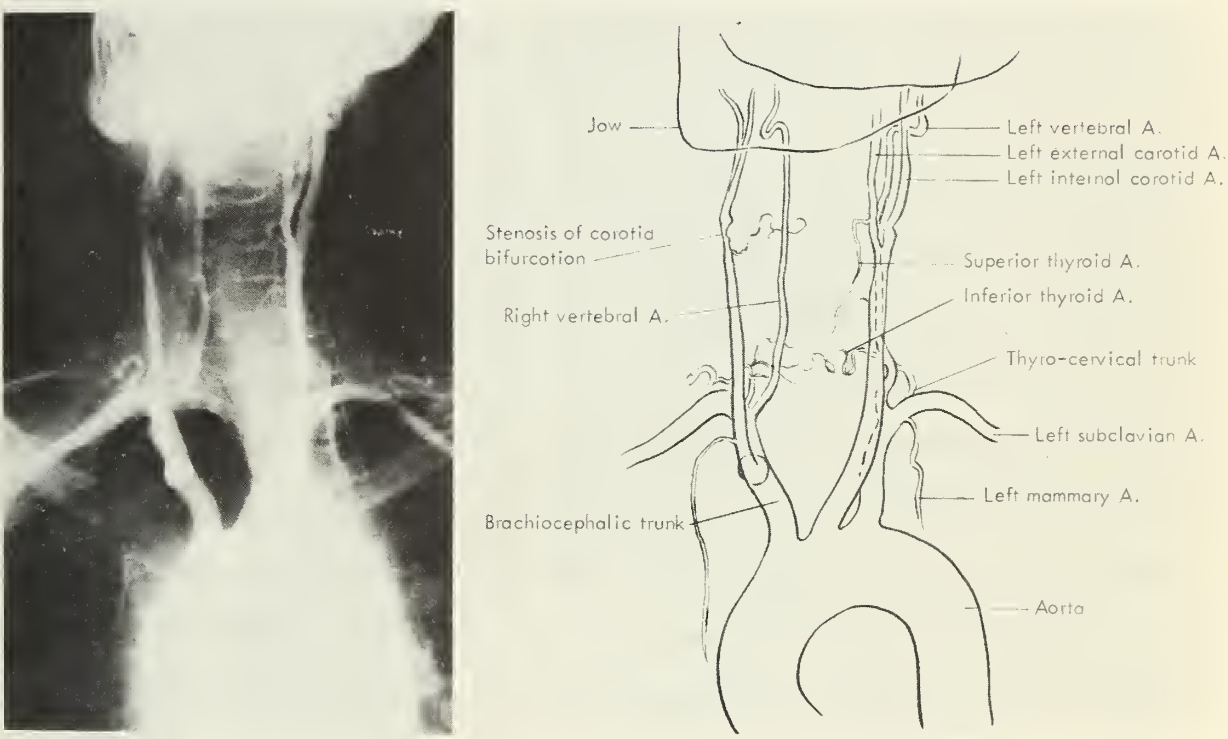
Another basic process is hypertension which appears to cause an accentuation of atherosclerosis and which may lead to vessel rupture and intracranial hemorrhage.

Cerebral arterial embolism and ischemia occur simultaneously or in rapid succession. These events may lead to hemorrhage if the embolic fragment becomes lysed and arterial pressure is restored into infarcted tissue.

Cerebrovascular Ischemia. When perfusion of focal areas of brain tissue is reduced below critical levels, tissue ischemia develops. If flow and pressure are restored before infarction develops, symptoms and signs of neurologic deficit resulting from the tissue ischemia subside. This sequence of events is called a transient ischemic attack.[1,2] In about one third of such cases these attacks herald cerebral infarction and as a consequence, tran-

FIGURE 1

Arch aortogram showing the anatomy of the aortocervical arteries. Lesions of this circulation are said to underlie about 40 percent of cerebral infarctions due to atherosclerosis.



sient ischemic attacks represent one of the best predictors for brain infarction (Figure 2).[2]

Transient ischemic attacks can occur either in the carotid or vertebral basilar arterial systems. In the carotid system the episodes are frequently the result of atheromatous plaques situated at the origin of the internal carotid artery in the neck. Such lesions can be treated surgically with a high degree of safety and with the likelihood of cure.[3-7] Plaques located in the subclavian-vertebral-basilar arterial circuit are more difficult to treat and the possible benefits of surgical therapy are less evident. Consequently, persons with vertebral-basilar insufficiency should be considered for treatment with long-term anticoagulation.

Brain Infarction. Disturbances of pressure or flow, oxygenation or glucose content of arterial blood can produce manifestations of brain ischemia within half a minute. When prolonged, infarction results. By far the most common cause of this sequence of events is end-stage cervicocranial atherosclerosis, which causes focal reduction in the lumen of the arteries supplying the brain. In other instances plaques accumulate thrombi which occlude the lumens or break off as emboli. Lastly, atheromatous plaques may ulcerate and discharge their grumous contents as microemboli. These complications are best prevented by use of anticoagulants or by surgical extirpation of atherosclerotic plaques.[8] About 40 percent of patients with brain infarction die of infarction or secondary complications (Figure 3).[3]

Brain Hemorrhage. Hemorrhage into the substance of the brain in adult life is usually a complication of prolonged systemic hypertension. Brain hemor-

FIGURE 2

Ulcerated plaques are thought to be the underlying mechanism in many transient ischemic attacks. These ulcerations are visible on arteriography in many cases.

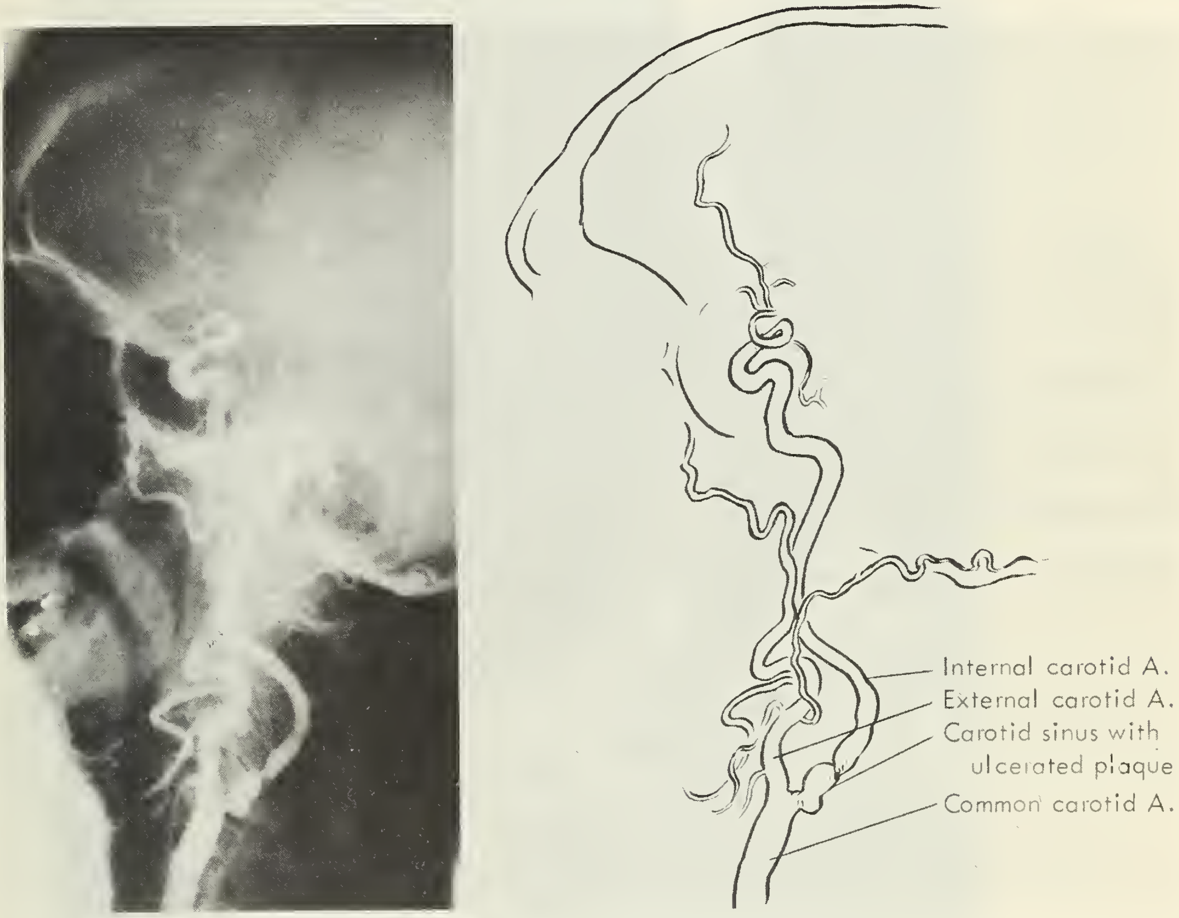
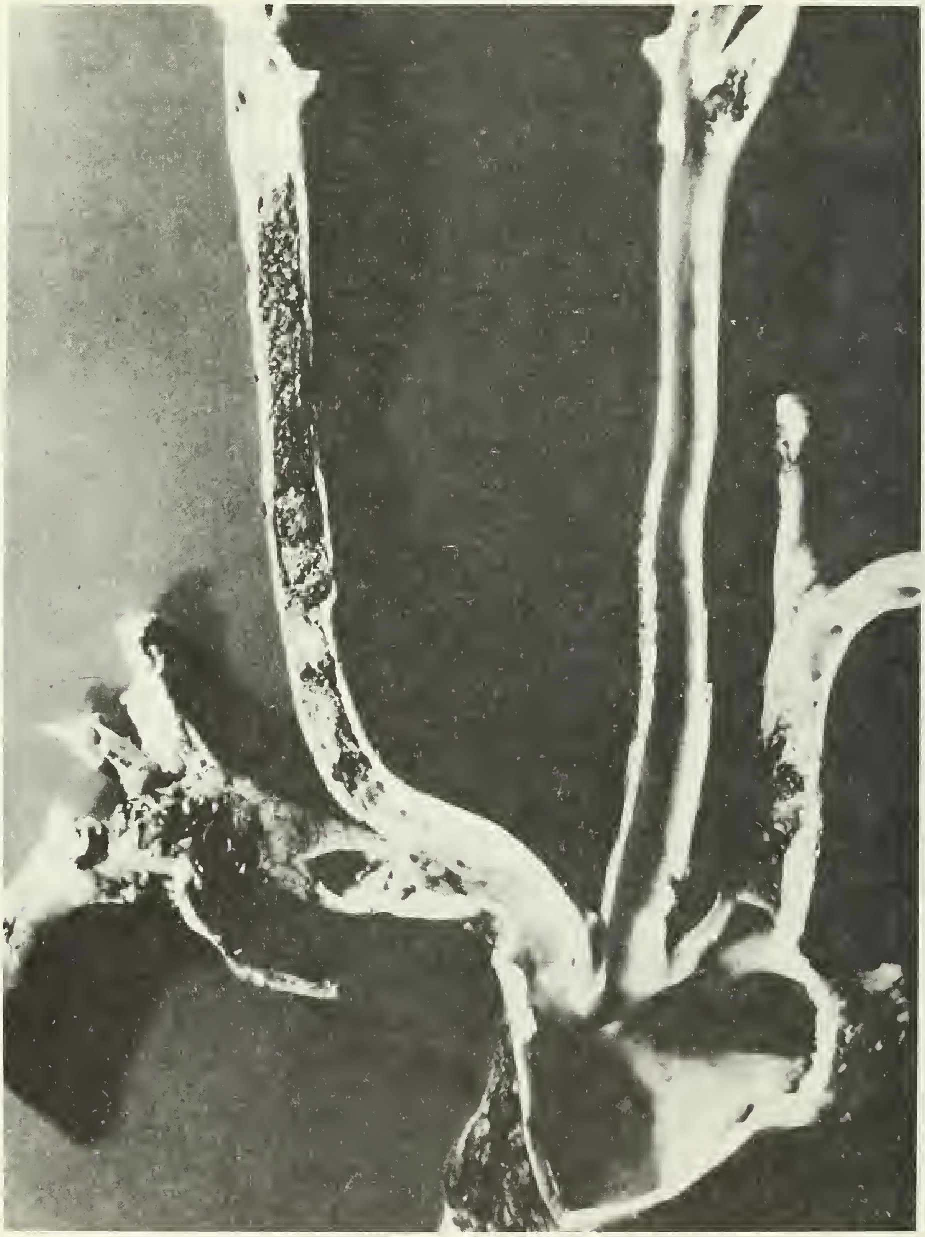


FIGURE 3

Advanced atherosclerotic changes in the aortocervical arteries accompanied by atherothrombosis of the right common carotid artery and the left internal carotid artery. Reprinted with the permission of the authors and the publishers from Cerebrovascular Disorders, James F. Toole and Aneel N. Patel, McGraw-Hill Co., 1967



rhage strikes without warning, is fatal in about 80 percent of cases, and its survivors are usually permanently disabled. These are all reasons why vigorous measures to identify and treat asymptomatic hypertensives are mandatory.

Unresolved Problems

Manifestations of cerebral ischemia and infarction are enormously variable; 1) because of the plethora of arteries nourishing the brain, each with its own area of brain to perfuse; 2) because the vascular supply varies to a certain degree among individuals; and 3) because of the tremendous variation from person to person in awareness of fleeting and often subtle phenomena which may herald overt cerebrovascular disease. For example, headache can be a symptom of impending cerebral infarction or hemorrhage, but who among the tens of millions who suffer with occasional headaches should be suspect? Furthermore, transient blurring of vision or dizziness may presage carotid or vertebral-basilar disease, but in whom among the many persons who have these occasional symptoms do these have clinical significance? Consequently, informed opinion varies on how stroke-prone individuals can best be identified from among these large populations of symptomatic persons.

There is general consensus that prophylactic measures should be instituted in persons who have one or several of the factors known to increase the risk of stroke such as heart disease, diabetes mellitus, hypertension, and/or transient ischemic episodes. Most investigators believe that there should be aggressive population screening programs to identify and treat susceptible individuals; however, some would wait until symptomatic individuals seek medical attention. At the present time, the proper course of action is not clear because adequate prospective data from screening programs are not available for making this judgment.

Every effort must be expended to prevent cerebral ischemia, to treat it aggressively and rapidly when it occurs, and to prevent its progression to cerebral infarction. This is an emergency situation regarding which neither the public nor health professionals are sufficiently informed.

The reasons for this widespread lack of awareness of the grave significance of the early manifestations of stroke are due to many diverse factors. Among them are the victim's lack of awareness of the extent of disability, his lack of pain and the fact that he may not look sick, all of which lull his family into complacency. Others include the attitude of hospital personnel who may reject stroke victims in favor of more "acute patients for whom something can be done." Some physicians and hospitals will not admit or treat stroke patients at all; while for others, they are elective admissions. In many institutions to which stroke patients are admitted, care is custodial only. These attitudes must change. Physicians must be made aware of the necessity and means for rapid accurate diagnosis and emergency management of stroke victims and put them into practice. Hospitals must develop systems for rapid accession of the patient to his proper location in the care delivery system. Specialized stroke care units must be developed, the primary purpose of which will be to sustain brain function and to minimize neural deficit in stroke victims. In order to accomplish this purpose, teams of specially trained health personnel headed by a physician and including representatives of various medical specialties, nurses and physical therapists, should be formed in centrally located institutions. These teams would render comprehensive care to stroke victims whose treatment at the present time is all too often fragmented and piecemeal.

Anticoagulant therapy to prevent recurrent episodes in patients with transient ischaemic attacks (TIAs) due to atherosclerotic cerebrovascular disease is well established.[9,10,11] Millikan[12] concludes that long term anticoagulant therapy significantly reduces the risk of cerebral infarction in patients with transient ischaemic attacks. However, there is a small but definite risk of cerebral or systemic hemorrhagic complications. The incidence of intracranial hemorrhage is related to the level of hypertension, while systemic hemorrhage is related to the presence of concomitant disease and to the duration of anticoagulant therapy. Unresolved problems include definitions of the level of hypertension that does not contraindicate anticoagulant therapy and the optimal duration of treatment.

The role of anticoagulation in halting the progression of cerebral infarction (stroke in evolution) is not clear, but the weight of evidence favors its use.[12]

For completed stroke, there is a difference of opinion regarding the use of anticoagulation[12] on a long term basis, for prophylaxis of recurrence. Anticoagulation is definitely hazardous because of the incidence of severe hemorrhage, but whether this is true for all anticoagulants or only for coumarin compounds is unknown.

Recommendations

1. Active investigation into ways to identify stroke-prone individuals should be given high priority. All screening programs for prevention of brain hemorrhage and infarction are dependent upon the development of such methods.

2. A program of education designed to heighten public awareness of the risk factors and warning symptoms and signs associated with brain infarction must be initiated.

3. Intensive medical school and postgraduate medical education must be undertaken to instruct all physicians caring for patients who may develop strokes in the techniques of early diagnosis and proper management.

4. Special care units must be developed to treat stroke patients intensively, using specially trained personnel.

5. The stroke team concept must be popularized and put into general use so that stroke victims can be quickly transported to specialized facilities.

6. Individuals with sustained hypertension must be identified early and treated vigorously in order to prevent brain hemorrhage.

7. The question of the use of anticoagulant therapy for the progressing cerebral infarction should be resolved by an appropriately designed study.

8. Studies should be carried out with antithrombotic agents other than coumarin derivatives to determine whether they can reduce recurrence rates without inducing hemorrhagic complications.

References

1. Toole JF, Patel AN: Cerebrovascular Disorders. New York, McGraw-Hill Book Co, 1967

2. Baker RN, Whisnant JP, Kuller L: Transient ischemic attacks. Transactions of the Seventh Princeton Conference on Cerebral Vascular Diseases. Edited by JF Toole, J Moossy, R Janeway. New York, Grune and Stratton, 1970, p 161-188

3. Wylie EJ, Ehrenfeld WK: Extracranial Occlusive Cerebrovascular Disease: Diagnosis and Management. Philadelphia, WB Saunders Co, 1970

4. Fields WS, Maslenikov V, Meyer JS, et al: Joint study of extracranial arterial occlusion: V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. JAMA 23:1993-2003, 1970

5. Bauer RB, Meyer JS, Fields WS, et al: Joint study of extracranial arterial occlusion: III. Progress report of controlled study of long-term survival in patients with and without operation. JAMA 208: 509-518, 1969

6. Blaisdell WF, Clauss RH, Galbraith G, et al: Joint study of extracranial arterial occlusion: IV. A review of surgical considerations. JAMA 209:1889-1895, 1969

7. Crawford ES, DeBakey ME, Morris GC Jr, et al: Surgical treatment of occlusion of the innominate, common carotid and subclavian arteries: A 10-year experience. Surgery 65:17-31, 1969

8. Siekert RG, Whisnant JP, Millikan CH: Surgical and anticoagulant therapy of occlusive cerebrovascular disease. Ann Intern Med 58: 637-641, 1970

9. Baker RN, Schwartz WS, Rose AS: Transient ischemic attacks: A report of a study of anticoagulant treatment. Neurology 16:841-847, 1966

10. Baker RN, Broward JA, Fang HC, et al: Anticoagulant therapy in cerebral infarction: Report on cooperative study. Neurology 12:823-835, 1962

11. Millikan CH: Anticoagulant therapy in cerebrovascular disease. Cerebral Vascular Diseases. Transactions of the Fourth Princeton Conference. Edited by RG Siekert, JP Whisnant. New York, Grune and Stratton, 1965, pp181-184.

12. Millikan CH: Anticoagulant therapy in cerebrovascular disease. Cerebrovascular Survey Report for Joint Council Subcommittee on Cerebrovascular Disease, National Institute Neurological Diseases and Stroke, and

National Heart and Lung Institute. Edited by RG Siekert. Rochester, Minn, revised July 1970,pp 218-225

General References

1. Acheson J, Hutchinson CE: Observations on the natural history of transient cerebral ischemia. Lancet 2:871-874, 1964

2. Adams GF, Merrett JD: Prognosis and survival in the aftermath of hemiplegia. Brit Med J 1:309-314, 1961

3. Baker AB, Kinnard J, Ianonne A: Cerebrovascular disease: VIII. Role of nutritional factors. Neurology 11:380-389, 1960

4. Baker RN, Ramseyer JC, Schwartz WS: Prognosis in patients with transient cerebral ischemic attacks. Neurology 18:1157-1165, 1968

5. Bauer RB, Meyer JS, Fields WS, et al: Joint study of extracranial arterial occlusion: III. Progress report of controlled study of long-term survival in patients with and without operation. JAMA 208: 509-518, 1969

6. Berkson DM, Stamler J: Epidemiological findings on cerebrovascular diseases and their implications. J Atheroscler Res 5:189-202, 1965

7. Carter AB: Strokes: Natural history and prognosis. Proc Roy Soc Med 56:483-486, 1963

8. Collins SD, Lehmann JL, Trantham KS: Major causes of illness of various severities and major causes of death in six age periods of life. US Department of Health, Education, and Welfare, Public Health Service. Washington DC, Public Health Reports, Public Health Monograph 30, 1955

9. David NJ, Heyman A: Factors influencing the prognosis of cerebral thrombosis and infarction due to atherosclerosis. J Chronic Dis 11: 394-404, 1960

10. Eisenberg H, Morrison JT, Sullivan P, et al: Cerebrovascular accidents --incidence and survival rates in a defined population, Middlesex County, Connecticut. JAMA 189:883-888, 1964

11. Friedman GD, Wilson WS, Mosier JM, et al: Transient ischemic attacks in a community. JAMA 210:1428-1434, 1969

12. Goldberg ID, Kurland LT: Mortality in 33 countries from diseases of the nervous sytem. World Neurology 3:444-465, 1962

13. Grunnet ML: Cerebral vascular disease: Diabetes and cerebral atherosclerosis. Neurology 13:486-491, 1963

14. Heyman A, Arons M, Quinn M, et al: The role of oral contraceptive agents in cerebral arterial occlusion. Neurology 19:519-524, 1969

15. Kuller L, Seltser R, Paffenbarger RS Jr, et al: Original contributions: Trends in cerebrovascular disease mortality based on multiple cause tabulation of death certificates 1930-1960: A comparison of trends in Memphis and Baltimore. Amer J Epidem 88:307-317, 1968

16. Kurland LT, Choi NW, Sayre GP: Current status of the epidemiology of cerebrovascular diseases. Stroke Rehabilitation: Basic Concepts and Research Trends. Edited by WS Fields, WA Spencer. St Louis, Missouri, Warren H Green Inc, 1967,pp 3-30

17. Marshall J: The natural history of transient ischaemic cerebrovascular attacks. Quart J Med 33:309-324, 1964

18. Marshall J, Kaeser AC: Survival after non-haemorrhagic cerebrovascular accidents: A prospective study. Brit Med J 2:73-77, 1961

19. Robinson RW, Cohen WD, Higano N, et al: Life-table analysis of survival after cerebral thrombosis--ten-year experience. JAMA 169:1149-1152, 1959

20. Robinson RW, Demirel M, LeBeau RJ: Natural history of cerebral thrombosis: Nine to nineteen year follow-up. J Chronic Dis 21:221-230, 1968

21. Sahs AL, Perret GE, Locksley HB, et al: Intracranial Aneurysms and Subarachnoid Hemorrhage: A Cooperative Study. Philadelphia, JB Lippincott Co, 1969, p 1070

22. Schroeder HA: The water factor. New Eng J Med 280:836-838, 1969

23. Seltser R: The epidemiology of cerebrovascular disease. Thrombosis. Edited by S Sherry, KM Brinkhous, E Genton, et al. Washington DC, National Academy of Sciences, 1969,pp 215-235

24. Kuller LH, Bolker A, Saslaw MS, et al: Nationwide cerebrovascular disease mortality study:

    I. Methods and analysis of death certificates. Amer J Epidem 90:536-544, 1969

    II. Comparison of clinical records and death certificates. Amer J Epidem 90:545-555, 1969

    III. Accuracy of the clinical diagnosis of cerebrovascular disease. Amer J Epidem 90:556-566, 1969

    IV. Comparison of the different clinical types of cerebrovascular disease. Amer J Epidem 90:567-578, 1969

25. Stamler J: Epidemiology of cerebrovascular disease. Proceedings of the National Stroke Congress. Edited by RE DeForrest. Springfield, Ill, Charles C. Thomas, 1966,pp 24-37

C. PERIPHERAL

Current State of Knowledge

The peripheral circulation, including the aorta and vessels to the abdominal viscera and the extremities, accounts for a significant fraction of all atherosclerotic vascular disease. Moreover, disease of these vessels is commonly associated with atherosclerotic lesions of the coronary and cerebral circulation.

1. Aorta: Aneurysm. Widening and tortuosity of the aorta and certain of its primary branches, the innominate and iliac arteries, are common among individuals beyond the fifth decade, especially in the presence of hypertension. These abnormalities are more diffuse than aneurysms which by contrast are more localized dilatations of the wall of the aorta, involving the entire circumference (fusiform) or one side of the vessel (saccular). Aneurysms may vary in size up to 15 or more centimeters in diameter. Aortograms are diagnostically deceptive and of limited usefulness in such cases because the demonstrable channel through the aneurysm may appear normal, since the rest of the aneurysm may be filled with layers of thrombus.

The prevalence of aneurysm among the general population is not known. One study[1] showed an incidence of 1.8 percent among 5,000 autopsies (dissecting aneurysms were excluded). The lesions are more commonly found in men than in women, the male to female ratio varying between two and 10 in different reports.

Until recent years, aneurysms in the thoracic or the immediately subdiaphragmatic aorta were commonly found to be syphilitic in origin. At present, however, syphilitic vascular lesions have become distinctly less common and most aortic aneurysms both above and below the diaphragm are atherosclerotic in origin.

Most aneurysms are asymptomatic in their early stages. Occasionally, patients become aware of the lesion in the abdomen on palpation of a pulsating mass during self-examination. When symptoms develop, the most common and compelling complaint is pain arising from interstitial dissection of blood, compression of adjacent nerve roots, and erosion into bone.

The most serious complications of aneurysm are progressive degeneration and thinning of the aneurysmal wall resulting in "leakage" of blood into the adjoining structures and eventually, in frank rupture of the wall and massive hemorrhage. Development of infection in the aneurysmal wall and among the lamellae of thrombus may occur. When syphilitic thoracic aneurysms were common, they would frequently erode through the sternum and bleed massively externally. More commonly, however, thoracic aneurysms, both syphilitic and atherosclerotic, erode into mediastinal structures and bleed massively into them. Erosion and hemorrhage into the pericardium lead to cardiac tamponade; into the trachea and main stem bronchus to fatal hemoptysis; and into the esophagus to massive upper gastrointestinal tract bleeding. In the abdomen, aneurysms of the aorta and iliac arteries may bleed into the retroperitoneal space or into the peritoneal cavity. Erosion into the vena cava results in hemodynamically serious arteriovenous fistulae.

Severe pain in a patient with aneurysm is presumptive evidence of leakage of blood and of impending massive hemorrhage. The latter is attended by hemorrhagic shock, often profound and fatal.

Life expectancy is reduced after the diagnosis of atherosclerotic aneurysm. In the absence of intervention very few patients live as long as 10 years after a diagnosis of abdominal aneurysm is made, one-third of such patients die within a year; and one-half within one to three years.[2]

Individuals with aneurysm of the aorta and its large branches are elderly, and although rupture of the aneurysm is a common cause of death, these patients are also subject to other fatal complications of atherosclerosis, such as myocardial infarction, stroke, congestive heart failure or other conditions.[3]

The treatment of aneurysm has excited the imagination of physicians and surgeons for centuries. Surgery offered rather little for this serious conditions until 1951, when Dubost successfully excised an aneurysm of the lower abdominal aorta and established continuity by the insertion of a preserved human aortic homograft.[4]

Many technical developments have taken place in this area of vascular surgery. Homografts, arterial and venous, have been replaced by devices constructed of synthetic fabrics. Partial rather than total excision of the aneurysm has led to reduction in operative morbidity and mortality. Significant improvements have been made in available suture materials and in the care of the critically ill. However, operative procedure for the correction of aneurysm carries a risk which must be considered in reaching a decision for surgical intervention. Any operative procedure for the correction of aneurysm carries a significant risk, magnified by the advanced age and associated disease common to the elderly persons having such disorders.

2. Mesenteric Arteries. As in the case of aneurysms and occlusive disease of other arteries, the true prevalence of atherosclerotic disease of the celiac artery and mesenteric arteries is not known, since the lesions are asymptomatic until serious compromise of blood flow to the abdominal viscera has occurred. In general, atherosclerotic involvement of the visceral arteries reflects involvement of the abdominal aorta. At autopsy these arteries are seldom commented upon unless gross resultant intestinal lesions are present.

Symptoms and signs attributable to aneurysmal or atherosclerotic obstructive disease of the inferior mesenteric artery are very rare because of the excellent collateral circulation of the colon. However, occlusive disease of the superior mesenteric artery leads to recognizable signs and symptoms of intestinal dysfunction which are sometimes dramatic. The superior mesenteric artery supplies nearly the entire small intestine and the proximal portion of the colon without significant collateral circulation. Among the elderly, weight loss and failure to gain weight have been attributed to poor mesenteric arterial circulation resulting in incomplete absorption of food substances. Abdominal pain may occur after eating, during periods of increased intestinal activity, and has been attributed to insufficient capacity of the superior mesenteric artery to provide blood for the additional requirement of the digestive process (abdominal "angina" or "claudication").

Acute complete occlusion of the superior mesenteric artery nearly always results in vascular collapse with gangrene of the entire small intestine including the cecum and parts of the adjoining colon, and generally excluding the fourth portion of the duodenum. Drastic changes take place in the distribution of body fluids. Blood extravasates into the peritoneal cavity, and toxic vaso-active substances are formed. Resection of the involved bowel carries a forbidding mortality. The condition has been called "abdominal apoplexy".

In recent years, in view of the known mortality rate from acute occlusion of the superior mesenteric artery (resulting from embolism or thrombosis), attempts have been made to diagnose the condition before infarction or irreversible changes have taken place in the intestine. Some success has been achieved. The first successful embolectomy from the superior mesenteric artery was reported in 1957.[5] The problems are two-fold and interdependent. Diagnosis must be made early within an hour or two from the time of onset of symptoms, but the surgeon is commonly hesitant for fear of performing an unnecessary laparotomy in a poor-risk, usually elderly patient with a questionable diagnosis.

3. Renal Arteries. Plaques not infrequently encroach upon the ostia of one or both renal arteries resulting in ischemia of the kidney. While this may not cause necrosis, it may well disturb certain elements of renal function. Atherosclerosis may also develop in the renal arteries

themselves. The result may be ischemia of the kidney leading to abnormal renal function or the elaboration of humoral substances leading to hypertension. In one study, aortography of 2,500 patients revealed 69 cases of renal artery stenosis, an incidence of 2.8 percent in that selected group.[6] Aneurysms of the renal artery, through hemorrhage and thrombosis, occasionally lead to renal ischemia and hypertension.

Interference with blood flow in arteries supplying one or both kidneys is likely to result in "renal hypertension", as first produced experimentally and described by Goldblatt nearly 40 years ago.[7] This sequel (hypertension) depends upon the presence of viable renal tissue with impaired circulation. The renin-producing juxtaglomerular apparatus serves as a pressure-sensitive organ which must be viable and responsive to decreased preglomerular arteriolar pressure and flow. A large amount of experimentation has been done to clarify the nature of the mechanisms for this kind of hypertension, and much information is now available concerning the role of aldosterone in the process. Except for the complications of hypertension, this degree of impairment of renal blood flow otherwise is asymptomatic. Among the causes of hypertension, as many as two to three percent may be attributable to relative renal ischemia.

Renal arterial occlusions resulting in infarction are asymptomatic when small. However, symptoms do develop when larger masses of renal tissue are involved, as the result of progressive narrowing of the main renal artery or its branches culminating in thrombosis, or as the result of emboli from ulcerating atherosclerotic plaques either in the aorta or in the renal arteries themselves. The symptoms vary according to the extent of the infarcts. Small infarcts may be felt as pain in the costovertebral angle of the back, the loin, or in the abdomen. Hematuria is detectable, either microscopic or gross, along with granular casts and white blood cells. Hypertension commonly develops when infarction does not involve the entire kidney, and the high blood pressure may be severe enough to require treatment.

Complete infarction of the kidneys is often fatal since the opposite kidney is usually involved at least to some extent by atherosclerosis, and occlusion and thrombosis of the renal arteries occasionally may be bilateral. When the lesions develop acutely, patients have very severe pain, and progress into vascular collapse which is often fatal.

Patients with complete infarction of the kidney have received only supportive treatment. Such cases theoretically could be amenable to surgical intervention if diagnosed prior to necrosis of the kidney. Safe diagnostic methods and other criteria for diagnosis need to be developed to make this possible.

Dramatic results have been reported from several clinics indicating cures of renal hypertension by direct arterial surgery correcting or circumventing the renal vascular obstruction, or by nephrectomy, when direct arterial surgery is not possible and the opposite kidney is functioning satisfactorily.[8,9,10]

4. Peripheral Arteries: General Considerations. The term peripheral circulation as used in this section refers to branches of the aortic arch and the vessels of the neck, upper and lower extremities.

Atherosclerosis involving the peripheral circulation becomes clinically apparent in two ways: 1) by causing intermittent pain when the diseased arteries are unable to meet the increased demand for blood by the tissues in response to increased activity or exercise (intermittent claudication); or 2) by resulting in diminution of blood flow to the point that the metabolic needs of organs and tissues are not met even at rest, and the patient experiences persistent pain (rest pain) or develops gangrene.

Intermittent claudication. The majority of patients with peripheral atherosclerosis have no symptoms when at rest, but are distressed when activity is undertaken which requires increased delivery of oxygen to the tissues. Ordinarily, the progressive enlargement of atheroma encroaching upon the lumen of an artery is accompanied by concomitant development of collateral circulation. The stimulus for the development of increased collateral circulation has not been identified, but appears to be related to a disproportion between need of the tissues for blood and that actually delivered by the circulation. When work is increased and greater circulatory delivery is required, the collateral circulation which has developed for meeting basal requirements is inadequate and the patient experiences intermittent claudication in the affected extremities.

Rest Pain. Occasionally the enlargement of atheroma is not attended by concomitant development of collateral circulation adequate to meet basal requirements. This may occur 1) if atherogenesis progresses unusually rapidly so that collateral vessels cannot keep up with the deterioration of main-channel blood flow; 2) if thrombosis and embolism complicate the atheroma; and 3) if for some fundamental reason (anatomic or metabolic) collateral vessels are not stimulated to develop. When the main channel for blood flow is seriously encroached upon by atheroma with or without thrombosis and embolization, and there is no adequate collateral circulation, the delivery of oxygen and nutrients and the removal of metabolic products are inadequate for normal metabolism. Thereupon, pain results when sensitive tissues are involved. Clinically, this situation is recognized as "rest pain" in the extremities.

Gangrene. Further progression of the atheroclerotic process without proportionate development of collateral circulation can result in non-viability of tissue. The clinical situation accordingly progresses from one in which rest pain is predominant, to one in which irreversible tissue necrosis (gangrene) takes place.

The majority of individuals with atherosclerosis of the peripheral arteries require only conservative management with careful and repeated instructions on care of the extremities. Tobacco is strongly contraindicated because of its vasoconstrictive action. If trauma and infection are avoided, development of collateral circulation usually continues apace with the progression of the atherosclerotic process.

However, the superimposition of any factor which acutely increases the need for delivery of blood as for example a need for healing a lesion caused by trauma or infection, adds an unattainable requirement, and gangrene supervenes.

Some patients who seek medical advice for symptoms caused by arterial insufficiency do require active measures to improve the peripheral circulation. A number of procedures of doubtful benefit have been recommended from time to time for this purpose.

A variety of pharmacologic agents also have been used for improving the arterial circulation through their vasodilator effects (alcohol, phenoxybenzamine, phentolamine, and nicotinyl tartrate). Some have been developed for their specific dilating effects on the circulation of skeletal muscle. While the circulatory increase caused by vasodilators is readily demonstrable experimentally and in subjects with normal circulation, the effectiveness in patients with significant obliterative arterial disease is difficult to demonstrate.

The demonstration by Royle (1924) that the extremities in patients with spastic paralysis showed evidence of increased circulation following sympathectomy led to the exploitation of sympathetic denervation of the extremities to produce vasodilation. This procedure was first used in patients with vasospasm (Raynaud's Disease; thrombo-angiitis with demonstrable spasm) and later in patients with obliterative atherosclerosis of the arteries.[11] Sympathectomy permits regional release of the circulation from neural vasoconstrictor effects, causes a decrease in local vascular resistance, and therefore, in selected cases, improves the arterial circulation.

Sympathectomy for vascular disease, especially in the lower extremity, remained popular until direct surgical intervention became possible as the result of the development of angiography, anticoagulation, and new suture materials.[12] Thromboendarterectomy was the earliest direct surgical procedure to effect restoration of main-channel arterial blood flow.[13] The procedure, with technical modifications, is commonly used at present either alone or in combination with other procedures.

The concept of bypassing an obliterative atherosclerotic lesion by means of a biologic or synthetic tube started with the work of Kunlin who employed the patient's own internal saphenous vein.[14,15] Tubes constructed from synthetic fabrics became popular because of their ready availability and ease of sterilization.[16] They are still widely used and are effective to bypass obstructions of large arteries, including the aorta itself.[17] For bypassing obstructions in the small arteries (including the femoral-popliteal system) the autogenous vein is considered preferable to synthetic prostheses and is recommended for this purpose by most surgeons.

Vasodilator drugs, sympathectomy, arterial reconstruction, and arterial bypass only enable the patient to make optimal use of his unobstructed blood vessels. Indeed, there is some evidence that relief or bypass of the arterial obstructing lesion may promote the development of atherosclerosis distal to the lesion. In general, however, the immediate improvement following reconstructive arterial surgery is dramatic. Late results are variable. More careful and objective follow-up studies are needed.

Unresolved Problems

More needs to be learned about aneurysms and their management, in particular those within the thorax. Methods need to be developed for objectively assessing the change in size of asymptomatic aneurysms. In the case of thoracic aneurysms, despite the employment of aortic bypass by means of the cardiopulmonary pump techniques, paraplegia is still an occasional complication of surgery. Hypothermia during surgery is not as frequently employed as it was a decade ago. Better methods for inducing it are needed. Most important are investigations of new approaches for pharmacologic techniques which will render tissues and organs (including the brain and spinal cord) more able to tolerate relative or complete ischemia.

More sophisticated methods of early diagnosis need to be developed. With additional experience, new diagnostic criteria may emerge and safer selective regional angiography may be developed. With the diagnosis established, including the site of the obliterative disease, corrective operations can be performed in patients with serious problems of intestinal absorption, abdominal angina, and early acute occlusion of the superior mesenteric artery by embolism or thrombosis.

Methods should be developed for preventing paraplegia as a complication of surgery for thoracic aneurysms. The problem concerns those patients in whom temporary occlusion of blood flow from the T-9 to T-12 segments is necessary. Pharmacologic depressors of brain and spinal cord metabolism should be sought.

Techniques for screening patients with hypertension need to be refined in order to identify those few who have lesions amenable to surgery. Methods for possible salvage of patients with complete renal artery occlusion need to be considered.

The nature of the return and persistence of hypertension following surgical procedures upon the renal arteries requires study.

The stimulus for the development of collateral circulation is unclear. Endocrine mechanisms (including growth hormone) could be involved. The problem is a very fruitful one for investigation.

Both the medical and lay communities are poorly informed as to the nature of atherosclerosis of the peripheral circulation and as to what can be done in terms of prevention of complications and symptomatic treatment in the present state of knowledge.

Recommendations

1. It is recommended that the natural history of atherosclerosis in the peripheral arteries be more critically defined by the application of techniques already available and other techniques to be developed.

2. Noninvasive techniques must be developed for the safe identification, localization, and examination of atherosclerotic lesions in the peripheral arteries.

3. Physiologic and pharmacologic adjuncts to surgery need to be developed in order to reduce morbidity and mortality.

4. Intensive studies of collateral circulation should be conducted to determine the nature of local and systemic factors which influence its development.

References

1. Carlsson J, Sternby NH: Aortic aneurysms. Acta Chir Scand 127: 466-473, 1964

2. Dennis EW, Kinard SA Jr, McCall BW, et al: Aneurysms of the aorta: A consideration of pre- and postoperative medical management. Progr Cardiovasc Dis 7:544-564, 1965

3. Cranley JJ, Herrmann, LG, Preuninger RM: Natural history of aneurysms of the aorta. Arch Surg 69:185-197, 1954

4. Dubost C, Allary M, Oeconomos N: A propos du proces-verbal. Mém Acad Chir (Paris) 77:381-383, 1951

5. Shaw RS, Rutledge RH: Superior-mesenteric-artery embolectomy in the treatment of massive mesenteric infarction. New Eng J Med 257: 595-598, 1957

6. Sutton D: Arteriography and renal artery stenosis. Postgrad Med J 42:183-187, 1966

7. Goldblatt H, Lynch J, Hanzal RF, et al: Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med 59:347-381, 1934

8. Poutasse EF, Dustan H: Urologic causes of hypertension: I. Hypertension due to renal artery disease. Cleveland Clin Quart 23:3-15, 1956

9. Poutasse EF: Diagnosis and treatment of occlusive renal artery disease and hypertension. JAMA 178:1078-1083, 1961

10. Morris GC Jr, DeBakey ME, Zinger LCC: Renovascular hypertension. Surg Clin N Amer 46:931-948, 1966

11. Simeone FA: Intravascular pressure, vascular tone, and sympathectomy. Surgery 53:1-18, 1963

12. Simeone FA: The role of sympathectomy in arterial disease. The Surgical Management of Vascular Disease. Edited by H Haimovici. Philadelphia, JB Lippincott Co, 1970, p 105-113

13. dos Santos JC: Sur la désobstruction des thromboses artérielles anciennes. Mém Acad Chir (Paris) 73:409-411, 1947

14. Kunlin J: Le traitement de l'artérite oblitérante par la greffe veineuse. Arch Mal Coeur 42:371-372, 1949

15. Kunlin J: Le traitement de l'ischémic artéritique par la greffe veineuse longue. Rev Chir Orthop 70:206-235, 1951

16. Edwards WS, Lyons C: Three years' experience with peripheral arterial grafts of crimped nylon and teflon. Surg Gynec Obstet 107:62-68, 1958

17. DeBakey ME: Basic concepts of therapy in arterial disease. JAMA 186:484-498, 1963

D. PULMONARY

Current State of Knowledge

Pulmonary arteriosclerosis, per se, produces no signs or symptoms. On the other hand, antecedent mechanisms, such as pulmonary hypertension or volume overload, may elicit a variety of clinical signs and symptoms, ranging from angina-like syndromes to breathlessness. Once arteriosclerosis of small vessels becomes severe, the vascular obliteration promotes further pulmonary hypertension.

Unresolved Problems

The major unresolved problem is the extent to which the obliterative arteriosclerotic lesions of the small vessels are reversible. Others are the same as for the presymptomatic state.

Recommendations

1. The general recommendations are similar to those of the presymptomatic state.

2. From the point of view of the symptomatic state, major attention should be directed to the natural history and reversibility of the arteriosclerotic lesions in the small vessels. Distinction should be emphasized between the responses of the intimal and medial components of the small vessels.

References

1. Liebow AA: Arteriosclerosis of the pulmonary circulation. Cowdry's Arteriosclerosis: A Survey of the Problem. Second Edition. Edited by HT Blumenthal. Springfield, Ill, Charles C Thomas, 1967, pp 248-328

2. Saldana ME, Harley RA, Liebow AA, et al: Experimental extreme pulmonary hypertension and vascular disease in relation to polycythemia. Amer J Path 52:935-981, 1968

3. Naeye RL, Vennart GP: The structure and significance of pulmonary plexiform structures. Amer J Path 36:593-605, 1960

4. Edwards JE: The Lewis A. Conner Memorial Lecture: Functional pathology of the pulmonary vascular tree in congenital cardiac disease. Circulation 15:164-196, 1957

5. Heath D, Brewer D, Hicken P: Cor Pulmonale in Emphysema: Mechanisms and Pathology. Edited by IN Kugelmass. Springfield, Ill, Charles C Thomas, 1968, p 114

VI. REHABILITATION

Current State of Knowledge

The Task Force wishes to emphasize that as contrasted with 25 years ago there has been great progress in recognizing the rehabilitation aspects of cardiovascular disease including illnesses due to atherosclerosis and its complications. The concept of rehabilitation of heart and stroke cases has received considerable exposure from the American Heart Association, federal, state and local agencies, industry, and from specialists in rehabilitation medicine.[1,2] Further, there are now available to patients facilities in every state and in most large urban communities for counseling, vocational training, and assistance in job placement. There are also in many but not all medical centers and in some community hospitals in-patient and out-patient services for rehabilitation of cardiovascular cases combining the talents of the internist, psychiatrist, occupational therapist, speech therapist, psychologist, social worker, and others. The record of reemployment of patients surviving a myocardial infarction and leaving the hospital is generally encouraging and in the range of 80-90 percent. In the case of patients with strokes, the rate of reemployment is much less favorable due in part to the older age of this population, to greater residual disability, and in some instances to the prolonged and often difficult process of recovery. Even in this case, however, the outlook for a return to a self-supporting existence is much brighter today than it was a quarter of a century ago.

Unresolved Problems

Despite the major advances noted above, problems still persist. There is too little awareness by the public and the medical profession of the role of rehabilitation in the total treatment and course of recovery of the patient who has had a heart attack or a stroke. Information presented to the Task Force indicates that approximately one-half of both the general public and of all physicians have little or no information regarding the availability of rehabilitation services.

Further, it appears that in medical schools, nursing schools, and post-graduate training programs, there has been inadequate emphasis on the teaching of rehabilitation. At these levels and also at the level of the practicing physician, there needs to be far more concentration on thinking of the process and needs of rehabilitation from the very onset of the acute illness. Too often, the specific medical problem is treated as one phase, and the rehabilitation aspects as a separate and much later phase. This unwarranted division of the illness into two components only serves to prolong mental and physical disability, and results in the application of rehabilitative techniques at a late and far from optimal time. The section on Overt Cerebral Atherosclerotic Disease describes the important role of the stroke team in assuring a prompt and broad therapeutic and rehabilitative approach to the individual who has had a cerebrovascular episode.

Although the rate of reemployment back to the former job of persons who have had a heart attack is encouraging (and less encouraging for patients with strokes), the record of employment by industry of a new employee who has a history of cardiovascular disease is much less satisfactory. Restraints imposed by fears of accidents by personnel managers, by policies of insurance carriers, and by judicial and industrial commission awards to persons alleged to have suffered cardiovascular episodes as the result of employment have presented formidable barriers to the cardiovascular patient seeking work. Even though "second injury" laws exist in some states, they are often not considered in employment practices.[3]

Recommendations

1. The rehabilitation aspects of heart attacks and strokes need to receive greater emphasis in the curricula of medical and nursing schools.

2. A greater effort should be made in hospital clinics and physicians' offices to ensure that considerations of rehabilitation needs are included in the initial evaluation of every patient admitted for treatment of arteriosclerotic disease and its complications.

3. Medical societies and hospital staffs must accept the obligation to keep the medical profession adequately informed as to the nature and availability of community rehabilitation services.

4. The Task Force recommends that the National Heart and Lung Institute, in conjunction with other government agencies, consider ways in which patients suffering from cardiovascular disability who receive financial support for an extended period of time from governmental or non-governmental sources may be automatically offered an opportunity of referral for rehabilitation.

5. The present application of Workmen's Compensation to patients with atherosclerotic disease and its complications is frequently not based on solid scientific evidence, and has resulted in unjustified barriers to the employment of the many citizens with a history or signs of cardiovascular disease. Therefore, the Task Force recommends that the National Heart

and Lung Institute in conjunction with other government agencies and representatives of the legal profession consider ways in which persons disabled by atherosclerotic diseases in the course of employment might best be covered by comprehensive insurance in order to obviate the delays, litigation, and ambiguities incident to the application of Workmen's Compensation.

References

1. Panel on "Medical Criteria for Employment Readiness:" Employability of workers handicapped by certain diseases: A guide for employers and physicians. Arch Environ Health 17:389-397, 1968

2. Warshaw LJ: Putting the patient with cardiac disease back to work. Arch Environ Health 12:651-654, 1966

3. Hellmuth GA, Rodey G, Johannsen WJ, et al: Work and heart disease in Wisconsin: I. Medical basis for Workmen's Compensation Awards over ten years. JAMA 198:9-15, 1966

VII. INVESTIGATOR INITIATED RESEARCH

It is clear from this report that very substantial progress has been made in many important areas of diagnosis and treatment of atherosclerosis and its complications. However, there are many vital, unanswered problems whose solutions are necessary to the conquest of these diseases. Throughout the report the Task Force has identified specific opportunities for basic and clinical research--opportunities which are likely to make an even greater impact on the understanding and treatment of atherosclerotic diseases in the future.

The one overriding conclusion from the recommendations offered above is that we do not as yet understand the basic mechanisms of atherogenesis. Since the answers to the cure of a disease are logically found in the discovery of its cause, the Task Force emphasizes the urgent need to expand the research base in atherosclerosis at many different levels. Among the major unresolved problems listed above are: 1) The genesis of the atherosclerotic lesion; 2) the relationship of lipids, lipoproteins, and diet to the development of atherosclerosis; 3) the role of thrombosis; 4) the etiology of essential hypertension and how hypertension contributes to the development of atherosclerosis and its clinical complications; 5) the way in which certain personal characteristics and habits occurring singly, and more importantly, in combination, are associated with an increased susceptibility to atherosclerosis; and 6) whether the atherosclerotic process is reversible in man.

The Task Force recommends that the National Heart and Lung Institute continue to support research into the pathogenesis of atherosclerosis with the specific goal of developing an integrated theory of causation, identifying primary and secondary factors, and their relative importance in the process of atherosclerosis, particularly in the development of its fatal sequelae.

Historical investigations have indicated that science does not necessarily develop in a gradual and orderly manner but that it proceeds through periods of great turmoil and sudden jumps in knowledge.[1] Similarly, the development of public health and medicine has proceeded in an irregular manner under the impact of new ideas from the basic sciences such as biology, physics, and chemistry.[2,3] These new ideas have revolutionized the concepts for the treatment of disease and decreased, through innovations in therapy and the abolition of costly and ineffective treatment, the economic burdens of disease. This dependence of modern medicine on new developments in the basic sciences has been evident in recent times. For example, in a recent survey of 22 articles announcing the development of a new drug, 56 percent of the references cited were to research work done in university laboratories and 87 percent of the citations were to journals and books in the basic sciences.[4]

Other evidence of the essential role played by basic research in the development of biomedical and other technologies is provided by a study undertaken by the Illinois Institute of Technology Research Institute in collaboration with the National Science Foundation.[5] The study traced the events leading to five major technological innovations. Of the 341 key events that contributed directly to these innovations, three-fourths were found to be motivated by the search for knowledge without regard for its immediate application.

In Appendix E the historical background of the development of lipoprotein typing is presented in a manner which illustrates how the contributions of scientists in disciplines unrelated to medicine have contributed to the development of this diagnostic technique now widely used in the classification and treatment of serum lipoprotein abnormalities.

The history of medical science is rich with other instances in which the results of unrelated research became crucial in the development of new diagnostic techniques or treatments. Such research is facilitated by providing gifted individuals with the freedom and resources to maintain optimal research activities under optimal conditions. Since the answers to atherosclerosis might lie outside the immediate field of atherosclerosis research as now conceived, the Task Force emphatically recommends adequate support of investigator-initiated research in all aspects of the biological and physical sciences, not just in those disciplines which may now be considered to be related. The magnitude of the support for fundamental investigations should be maintained in proportion to the total mission of the Institute, a proportion that is adequate to maintain a constantly improving scientific base to medical practice and a reservoir of ideas and manpower that will assure the best possible long-term performance of the health delivery system.

Recommendation

The Task Force strongly recommends adequate support of investigator-initiated, fundamental research in the biological and physical sciences.

References

1. Kuhn TS: The Structure of Scientific Revolutions. Second Edition, Enlarged. The University of Chicago Press, 1970, p 210

2. Handler P, Editor: Biology and the Future of Man. New York, Oxford University Press, 1970, p 928

3. Handler P, Editor: The Life Sciences. Washington DC, National Academy of Sciences, 1970, p 530

4. A Report on Basic Research in U.S. Chemistry by the Committee for the Survey of Chemistry: Chemistry: Opportunity and Needs. Washington DC, National Academy of Sciences - National Research Council, 1965, NAS-NRC Publication No 1292, p 85

5. ITT Research Institute: Volume I: Technology in Retrospect and Critical Events in Science. Chicago, The Illinois Institute of Technology Research Institute, 1968, p 104

APPENDIX A

ACKNOWLEDGEMENTS

In submitting its report, the National Heart and Lung Institute Task Force on Arteriosclerosis received assistance from the panel members listed in Appendix B and from the following individuals: Dr. Hugh A. McAllister, Armed Forces Institute of Pathology; Dr. Joseph L. Goldstein, University of Washington; and Dr. David C. Jenkins, University of North Carolina.

Statistical data were supplied by Mrs. Barbara S. Cooper and Mrs. Dorothy Rice, Social Security Administration, Department of Health, Education, and Welfare; Messrs. Dean E. Krueger, Abraham L. Ranofsky, Charles Wilder, and Ronald W. Wilson, National Center for Health Statistics, Public Health Service, Department of Health, Education, and Welfare; Mr. Mort Robins, Regional Medical Programs Service, Public Health Service, Department of Health, Education, and Welfare; and Mr. Stephen Schappel, Lea Associates, Inc.

The Fogarty International Center sponsored a trip to Europe by a subcommittee of the Task Force to seek the advice and assistance of the following individuals and their associates: Dr. S. G. Owen, Medical Research Council, London, England; Dr. Z. Pisa, World Health Organization, Copenhagen, Denmark; Professor G. Biorck, Serafimer Hospital, Stockholm, Sweden; Dr. M. Tottie, Head, Division of Information and International Cooperation, National Board of Health and Welfare, Stockholm, Sweden; and Professor L. Werko, University of Gothenburg, Gothenburg, Sweden.

APPENDIX B

NAMES OF PANEL MEMBERS

A. SPECIAL PANEL TOPICS AND CHAIRMEN

PANELS	CHAIRMEN
Cerebrovascular Disease	James F. Toole, M.D.
Clotting, Thrombosis and Hemorrhage	Kenneth M. Brinkhous, M.D.
Coronary Artery Disease	Charles K. Friedberg, M.D.
Diet	Elliot V. Newman, M.D.
Diet Heart Study Protocol	Oglesby Paul, M.D.
Drug Therapy in Hyperlipoproteinemia	Howard A. Eder, M.D.
Economic Aspects of Arteriosclerosis	Isadore Rosenfeld, M.D.
Exercise	T. Joseph Reeves, M.D.
Hyperlipidemia	Donald S. Fredrickson, M.D.
Hypertension	Oglesby Paul, M.D.
Lesion	Jack C. Geer, M.D.
Multiple Risk Factor Intervention Trials	Oglesby Paul, M.D.
Pediatric Arteriosclerosis	Sidney Blumenthal, M.D.
Peripheral Vascular Disease	Fiorindo A. Simeone, M.D.
Risk Factors	Ernest L. Wynder, M.D.
Social Aspects of the Rehabilitation of Cardiovascular Patients	Oglesby Paul, M.D.

B. CEREBROVASCULAR DISEASE PANEL PARTICIPANTS

William Blaisdell, M.D.
Chief of Surgery
San Francisco General Hospital
San Francisco, California

James Halsey, M.D.
Associate Professor and Director
Division of Neurology
University of Alabama
School of Medicine
Birmingham, Alabama

Richard Janeway, M.D.
Associate Professor of Neurology
Bowman-Gray School of Medicine
Winston-Salem, North Carolina

Clark Millikan, M.D.
Professor
Section on Neurology
Mayo Clinic
Rochester, Minnesota

C. CLOTTING, THROMBOSIS, AND HEMORRHAGE PANEL PARTICIPANTS

Marion Barnhart, Ph.D.
Professor of Physiology
and Pharmacology
Wayne State University
School of Medicine
Detroit, Michigan

Gustave Born, M.D.
Royal College of Surgeons
London, England

Ariel Loewy, Ph.D.
Professor of Biology
Haverford College
Haverford, Pennsylvania

George D. Penick, M.D.
Chairman, Department of Pathology
University of Iowa
School of Medicine
Iowa City, Iowa

Oscar D. Ratnoff, M.D.
Professor of Medicine
Western Reserve University
Cleveland, Ohio

Sol Sherry, M.D.
Professor and Chairman
Department of Medicine
Temple University School of Medicine
Philadelphia, Pennsylvania

Sanford Wessler, M.D.
Professor of Medicine
Washington University School of
Medicine
St. Louis, Missouri

Benjamin W. Zweifach, Ph.D.
Professor of Bioengineering
University of California
San Diego, California

D. CORONARY ARTERY DISEASE PANEL PARTICIPANTS

Robert Bruce, M.D.
Professor of Medicine
University of Washington School of Medicine
Seattle, Washington

Richard V. Ebert, M.D.
Professor and Head of the Department of Medicine
University of Minnesota School of Medicine
Minneapolis, Minnesota

Stephen E. Epstein, M.D.
Chief, Cardiology Branch
National Heart and Lung Institute
Bethesda, Maryland

Peter Frommer, M.D.
Chief, Myocardial Infarction Branch
National Heart and Lung Institute
Bethesda, Maryland

William J. Grace, M.D.
Director
Department of Medicine
St. Vincent's Hospital
New York, New York

Thomas Killip, III, M.D.
Chief, Division of Cardiovascular Diseases
Cornell University Medical Center
New York, New York

John W. Kirklin, M.D.
Chairman, Department of Surgery
University of Alabama Medical Center
Birmingham, Alabama

Charles A. Sanders, M.D.
Chief, Cardiac Catheterization Unit
Massachusetts General Hospital
Boston, Massachusetts

Stewart Wolf, M.D.
Director
The Marine Biomedical Institute
Galveston, Texas

E. DIET PANEL PARTICIPANTS

Edward H. Ahrens, Jr., M.D.
Professor
The Rockefeller University
New York, New York

Jerome Cornfield
Research Professor of Biostatistics
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania

Seymour Dayton, M.D.
Chief of the Medical Service
Wadsworth Hospital
Los Angeles, California

Ivan D. Frantz, Jr., M.D.
Clark Research Professor
University of Minnesota
School of Medicine
Minneapolis, Minnesota

Tavia Gordon
Statistician
Biometrics Research Branch
National Heart and Lung Institute
Bethesda, Maryland

Jerome G. Green, M.D.
Associate Director
Extramural Research and Training
National Heart and Lung Institute
Bethesda, Maryland

George V. Mann, Sc.D., M.D.
Associate Professor, Biochemistry
and Medicine
Vanderbilt University
School of Medicine
Nashville, Tennessee

Campbell Moses, M.D.
Medical Director
American Heart Association
New York, New York

Frederick J. Poats
Leader, Utilization Economics
Research Group
Department of Agriculture
Washington, D.C.

Paul A. Putnam, Ph.D.
Branch Chief
Beef Cattle Research
Department of Agriculture
Beltsville, Maryland

Eldon E. Rice, Ph.D.
Senior Nutritionist
Swift and Company
Oak Brook, Illinois

Henry Simmons, M.D.
Director of the Bureau of Drugs
Food and Drug Administration
Rockville, Maryland

Jeremiah Stamler, M.D.
Executive Director
Chicago Health Research Foundation
Chicago, Illinois

Malcolm Stephens
President
Institute of Shortening and
Edible Oils, Incorporated
Washington, D.C.

Virgil O. Wodicka, Ph.D.
Director, Bureau of Foods,
Pesticides and Product Safety
Food and Drug Administration
Washington, D.C.

F. DIET-HEART STUDY PROTOCOL PANEL PARTICIPANTS

Edward H. Ahrens, Jr., M.D.
Professor
The Rockefeller University
New York, New York

William E. Connor, M.D.
Professor of Internal Medicine
University of Iowa
Iowa City, Iowa

Jerome Cornfield
Research Professor of Biostatistics
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania

Frederick H. Epstein, M.D.
Professor of Epidemiology
University of Michigan
School of Public Health
Ann Arbor, Michigan

Ivan D. Frantz, Jr., M.D.
Clark Research Professor
University of Minnesota
School of Medicine
Minneapolis, Minnesota

Max Halperin, Ph.D.
Chief, Biometrics Research Branch
National Heart and Lung Institute
Bethesda, Maryland

G. DRUG THERAPY IN HYPERLIPOPROTEINEMIA PANEL PARTICIPANTS

Daniel Azarnoff, M.D.
Professor of Medicine and Pharmacology
University of Kansas Medical Center
Kansas City, Kansas

Marion Finkel, M.D.
Deputy Director, Bureau of Drugs
Food and Drug Administration
Rockville, Maryland

Donald S. Fredrickson, M.D.
Director of Intramural Research
National Heart and Lung Institute
Bethesda, Maryland

Robert H. Furman, M.D.
Executive Director
Clinical Research
The Eli Lilly Company
Indianapolis, Indiana

Scott Grundy, M.D., Ph.D.
The Rockefeller University
New York, New York

Richard Havlik, M.D.
National Heart and Lung Institute
Bethesda, Maryland

Daniel Steinberg, M.D., Ph.D.
Professor of Medicine
University of California School of Medicine
La Jolla, California

H. ECONOMIC ASPECTS OF ARTERIOSCLEROSIS

PANEL PARTICIPANTS

Herbert P. Galliher, Ph.D.
Professor
Department of Industrial Engineering
University of Michigan
Ann Arbor, Michigan

Herbert E. Klarman, Ph.D.
Professor
Graduate School of Public Administration
New York University
New York, New York

Dorothy Rice
Chief, Health Insurance Research Branch
Office of Research and Statistics
Social Security Administration
Washington, D.C.

I. EXERCISE PANEL PARTICIPANTS

Samuel M. Fox, III, M.D.
Cardiologist
Regional Medical Programs
Bethesda, Maryland

Herman K. Hellerstein, M.D.
Associate Professor of Medicine
Case Western Reserve University
School of Medicine
Cleveland, Ohio

Henry L. Taylor, Ph.D.
Professor of Physiology
University of Minnesota
Minneapolis, Minnesota

J. HYPERLIPIDEMIA AND PREMATURE ARTERIOSCLEROSIS PANEL PARTICIPANTS

Edwin L. Bierman, M.D.
Professor of Medicine
University of Washington
Seattle, Washington

David H. Blankenhorn, M.D.
Professor of Medicine
University of Southern California
Los Angeles, California

William Castelli, M.D.
Framingham Heart Disease
Epidemiology Study
National Heart and Lung Institute
Framingham, Massachusetts

William E. Conner, M.D.
Professor of Internal Medicine
University of Iowa
Iowa City, Iowa

Gerald R. Cooper, M.D.
Chief, Medical Laboratory Section
Communicable Disease Center
Atlanta, Georgia

Theodore Cooper, M.D.
Director
National Heart and Lung Institute
Bethesda, Maryland

Seymour Dayton, M.D.
Chief, Medical Service
Veterans Administration Center
Wadsworth Hospital
Los Angeles, California

Ivan D. Frantz, Jr., M.D.
Clark Research Professor
University of Minnesota
School of Medicine
Minneapolis, Minnesota

Donald S. Fredrickson, M.D.
Director, Intramural Research
National Heart and Lung Institute
Bethesda, Maryland

William Friedewald, M.D.
Clinical Evaluation and
Therapeutics Branch
National Heart and Lung Institute
Bethesda, Maryland

DeWitt S. Goodman, M.D.
Professor of Medicine
College of Physicians and Surgeons
Columbia University
New York, New York

Richard J. Havel, M.D.
Professor of Medicine
Cardiovascular Research Institute
University of California
San Francisco, California

Peter Kuo, M.D.
Associate Professor of Medicine
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

Robert S. Lees, M.D.
Director, Clinical Research Center
Massachusetts Institute of
Technology
Cambridge, Massachusetts

Robert I. Levy, M.D.
Lipid Metabolism Branch
National Heart and Lung Institute
Bethesda, Maryland

Robert P. Noble, M.D.
Sharon Research Institute
Sharon, Connecticut

Isadore Rosenfeld, M.D.
Clinical Associate Professor
of Medicine
Cornell University Medical College
New York, New York

Daniel Steinberg, M.D., Ph.D.
Professor of Medicine
University of California
San Diego
La Jolla, California

K. HYPERTENSION PANEL PARTICIPANTS

Quentin B. Deming, M.D.
Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Harriet P. Dustan, M.D.
Research Division
Cleveland Clinic Foundation
Cleveland, Ohio

Edward D. Freis, M.D.
Senior Medical Investigator
Washington Veterans Administration Hospital
Washington, D.C.

Edward Kass, M.D.
Director of the Channing Laboratory
Boston City Hospital
Boston, Massachusetts

John H. Laragh, M.D.
Professor of Clinical Medicine
Columbia University College of Physicians and Surgeons
New York, New York

H. Mitchell Perry, M.D.
Associate Professor of Medicine
Washington University School of Medicine
St. Louis, Missouri

Louis Tobian, M.D.
Professor of Medicine
University of Minnesota Medical School
Minneapolis, Minnesota

L. LESION PANEL PARTICIPANTS

Thomas B. Clarkson, D.V.M.
Head of Department of Laboratory
and Animal Medicine
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Paris Constantinides, M.D., Ph.D.
Professor of Pathology
University of British Columbia
Vancouver, British Columbia

Maria Daria Haust, M.D.
Professor of Pathology
University of Western Ontario
London, Ontario

Henry C. McGill, Jr., M.D.
Chairman, Department of Pathology
South Texas Medical School
San Antonio, Texas

Robert F. Scott, M.D.
Professor of Pathology
Albany Medical College
Albany, New York

William V.S. Still, M.D.
Professor of Pathology
Medical College of Virginia
Richmond, Virginia

Jack P. Strong, M.D.
Professor and Chairman
Department of Pathology
Louisiana State University
School of Medicine
New Orleans, Louisiana

Robert W. Wissler, M.D., Ph.D.
Professor and Chairman
Department of Pathology
University of Chicago School
of Medicine
Chicago, Illinois

M. MULTIPLE RISK FACTOR INTERVENTION TRIALS PANEL PARTICIPANTS

Jerome Cornfield
Research Professor of Biostatistics
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania

Howard A. Eder, M.D.
Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Ivan D. Frantz, Jr., M.D.
Clark Research Professor
University of Minnesota
School of Medicine
Minneapolis, Minnesota

Donald S. Fredrickson, M.D.
Director of Intramural Research
National Heart and Lung Institute
Bethesda, Maryland

Charles Friedberg, M.D.
Clinical Professor of Medicine
Mount Sinai School of Medicine
New York, New York

Herbert P. Galliher, Ph.D.
Professor
Department of Industrial Engineering
University of Michigan
Ann Arbor, Michigan

Max Halperin, Ph.D.
Chief, Biometrics Research Branch
National Heart and Lung Institute
Bethesda, Maryland

Harold W. Schnaper, M.D.
Professor of Medicine
School of Medicine
University of Alabama
Birmingham, Alabama

Asher Segall, M.D.
Associate Professor of Epidemiology
Harvard School of Public Health
Boston, Massachusetts

S. Leonard Syme, Ph.D.
Professor of Epidemiology
School of Public Health
University of California
Berkeley, California

Jeremiah Stamler, M.D.
Executive Director
Chicago Health Research Foundation
Chicago, Illinois

Ernest L. Wynder, M.D.
President
American Health Foundation
New York, New York

N. PEDIATRIC ARTERIOSCLEROSIS PANEL PARTICIPANTS

Allan Drash, M.D.
Director, Clinical Study Center
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Robert I. Levy, M.D.
Chief, Lipid Metabolism Branch
National Heart and Lung Institute
Bethesda, Maryland

Victor A. McKusick, M.D.
Professor of Medicine
Johns Hopkins University
School of Medicine
Baltimore, Maryland

Edmond A. Murphy, M.D., Sc.D.
Associate Professor of Medicine
Johns Hopkins University
School of Medicine
Baltimore, Maryland

O. PERIPHERAL VASCULAR DISEASE PANEL PARTICIPANTS

George F. Cahill, Jr., M.D.
Director
Joslin Research Laboratory
Boston, Massachusetts

Michael E. DeBakey, M.D.
President
Baylor University College
of Medicine
Houston, Texas

Donald E. Strandness, Jr., M.D.
Associate Professor of Surgery
University of Washington
School of Medicine
Seattle, Washington

Travis Winsor, M.D.
Associate Professor of Medicine
University of Southern California
Los Angeles, California

P. RISK FACTORS PANEL PARTICIPANTS

Joseph T. Doyle, M.D.
Head, Division of Cardiology
Albany Medical College
Albany, New York

William B. Kannel, M.D.
Director, Heart Disease
Epidemiology Study
National Heart and Lung Institute
Framingham, Massachusetts

Jessie Marmorston, M.D.
Clinical Professor of Medicine
University of Southern California
Los Angeles, California

Ralph S. Paffenbarger, M.D.
Chief, Bureau of Adult Health
and Chronic Diseases
California State Department
of Public Health
Berkeley, California

Q. SOCIAL ASPECTS OF THE REHABILITATION OF CARDIOVASCULAR PATIENTS

PANEL PARTICIPANTS

Sydney Croog, Ph. D.
Associate Professor of Sociology
Harvard School of Public Health
Boston, Massachusetts

Philip A. Klieger, M.D.
Associate Clinical Professor of
Physical Medicine and Rehabilitation
George Washington and Georgetown
Universities Medical Schools
Washington, D.C.

Paul Messmer
Assistant Executive Secretary for State Relations
President's Committee on Employment of
the Handicapped
United States Department of Labor
Washington, D.C.

Donald Ream
Workmen's Compensation Consultant
Bureau of Labor Standards
United States Department of Labor
Washington, D.C.

Paul Thomas
Executive Secretary
Medical Research Study Section
Social and Rehabilitation Service
Washington, D.C.

APPENDIX C

THE MAGNITUDE OF THE PROBLEM

It is evident, as stated throughout the entire report, that arteriosclerosis has both preclinical and clinical manifestations. In this section only the clinical aspects will be presented in terms of mortality and morbidity since the data on the preclinical aspects are not considered statistically reliable.

Diseases of the cardiovascular system for which statistics are compiled include the subgroups listed below according to the relative importance of arteriosclerosis as the underlying process. Each subgroup is identified by the code numbers of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD).[1] The category "congenital malformations of the circulatory system" is included in the broad category "congenital malformations" and is therefore not included as a subgroup of the cardiovascular diseases.

1. Arteriosclerotic and degenerative heart disease (ICD 420-422).

   The largest component is "arteriosclerotic heart disease, including coronary disease" (ICD 420), to which most fatal heart attacks and sudden coronary deaths are classified. To improve the comparability of mortality between geographic areas and the validity of long-term mortality trends, the components "chronic endocarditis not specified as rheumatic" (ICD 421) and "other myocardial degeneration" (ICD 422) are combined with "arteriosclerotic heart disease including coronary disease" (ICD 420), in the statistical compilations that follow.

2. Vascular lesions affecting the central nervous system (ICD 330-334). This subgroup corresponds closely to the category of stroke, including cerebrovascular occlusion, cerebral infarction and cerebral hemorrhage.

3. Diseases of the arteries (ICD 450-456). This subgroup includes most of the diagnostic categories in atherosclerosis of the aorta and peripheral vascular arteriosclerosis. It also includes non-atherosclerotic diseases such as Raynaud's disease, thromboangiitis obliterans, and gangrene of unspecified cause. Some of its components are not characterized by diagnostic criteria, for example, "general arteriosclerosis" (ICD 450) which is its largest component.

4. Hypertensive heart disease and other hypertensive disease (ICD 440-447). This subgroup is closely related to arteriosclerosis because of the fact that hypertension is a risk factor for clinical manifestations of arteriosclerosis, and for deaths that may be classified under other subgroups.

5. Other diseases of the heart (ICD 430-434). Arteriosclerosis underlies only some of the many components of this subgroup, especially congestive heart failure.

6. Rheumatic fever and chronic rheumatic heart disease (ICD 400-416). This subgroup is not a manifestation of arteriosclerosis, and is excluded in the data tabulations.

7. Diseases of veins and other diseases of the circulatory system (ICD 460-468). This subgroup is not a manifestation of arteriosclerosis, and is excluded in the data tabulations.

MORTALITY FROM ARTERIOSCLEROSIS

National mortality statistics are the tabulation of the underlying cause of death entered on each death certificate filed in the United States, the cause of death being coded to the International Statistical Classification of Diseases, Injuries, and Causes of Death. These statistics which are presented below are the most impressive, the most reliable and the most readily available measure of the nation's problem of arteriosclerosis. It should be pointed out, however, that mortality statistics are not precise measures because of the problem of accuracy of diagnostic information on death certificates and the weakness inherent in the concept of a single underlying cause of death.

Diseases of the Cardiovascular System

In 1967, 54.1 percent of all deaths were attributed to diseases of the cardiovascular system (Figure 1, Table 1). Of importance to our nation in terms of manpower and economic productivity, 30.5 percent of all deaths in the 35 to 44 year age group were due to these diseases (Figure 2). This percentage increases with advancing age so that these diseases account for 70.3 percent of the deaths among persons age 75 years and over. It is important to note that more than one-third of all deaths for persons under age 65 are due to cardiovascular diseases.

Arteriosclerosis and related diseases such as hypertension account for the major portion of deaths from cardiovascular disease (Figure 3). Virtually all arteriosclerotic and degenerative heart disease is due to atherosclerosis, as is most aortic and peripheral arterial disease. A large proportion of strokes

FIGURE 1

Percent Distribution of Deaths From Specific Causes To Deaths From All Causes, United States, 1967[2]

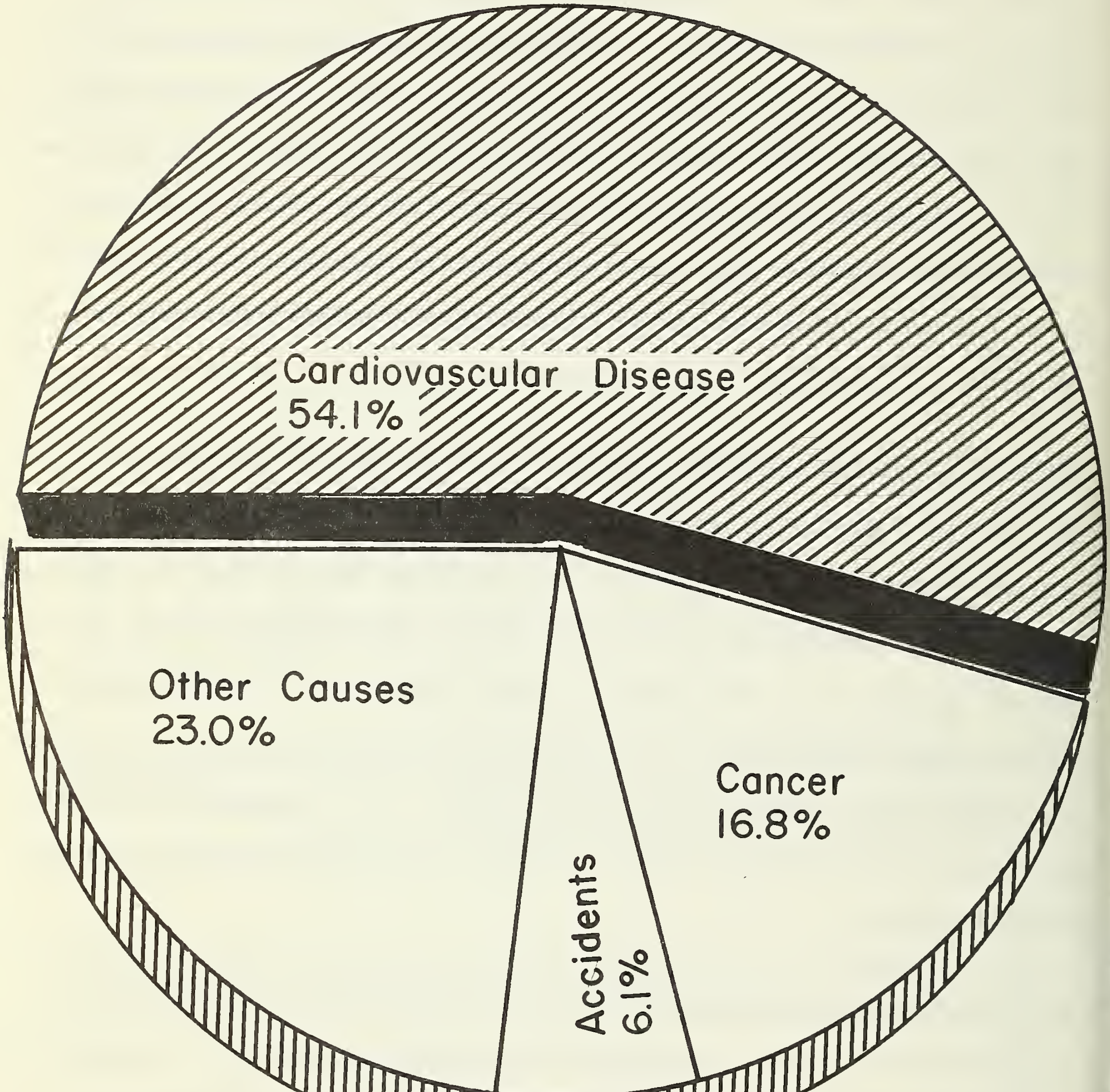


TABLE 1

Number of Deaths by Cause of Death and Broad Age Groups United States, 1967[2]

Cause of Death	All ages	Under age 65	Age 65 and Over*
All Causes	1,851,323	715,161	1,136,162
Cardiovascular diseases (330-334, 400-468)	1,002,111	250,977	751,134
Arteriosclerotic and degenerative heart diseases (420-422)	625,850	167,495	458,355
Vascular lesions affecting central nervous system (330-334)	202,184	36,761	165,423
Diseases of arteries (450-456)	53,326	6,911	46,415
Hypertensive heart disease and hypertension (440-447)	61,126	15,542	45,584
Other diseases of the heart (430-434)	31,267	10,302	20,965
Rheumatic fever and rheumatic heart disease (400-416)	14,176	8,930	5,246
Diseases of the veins and other diseases of the circulatory system (460-468)	14,182	5,036	9,146
Other Causes of Death	849,212	464,184	385,028

* Includes age not stated

Note: Numbers in parenthesis are codes of the International Classification of Diseases, Seventh Revision

FIGURE 2

Percent Breakdown of Deaths from Cardiovascular Disease to Deaths from all Causes by Age Group, United States, 1967[2]

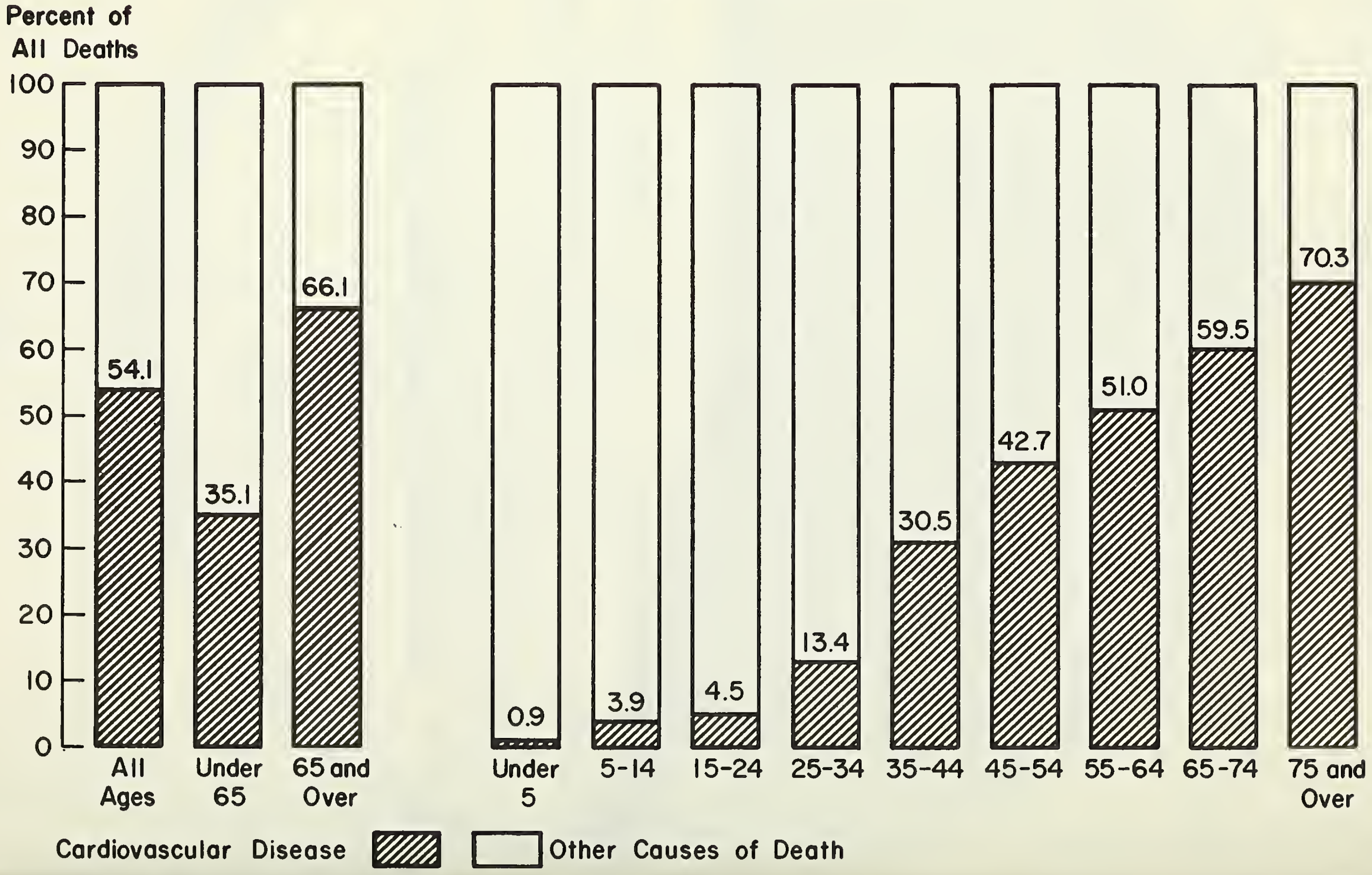
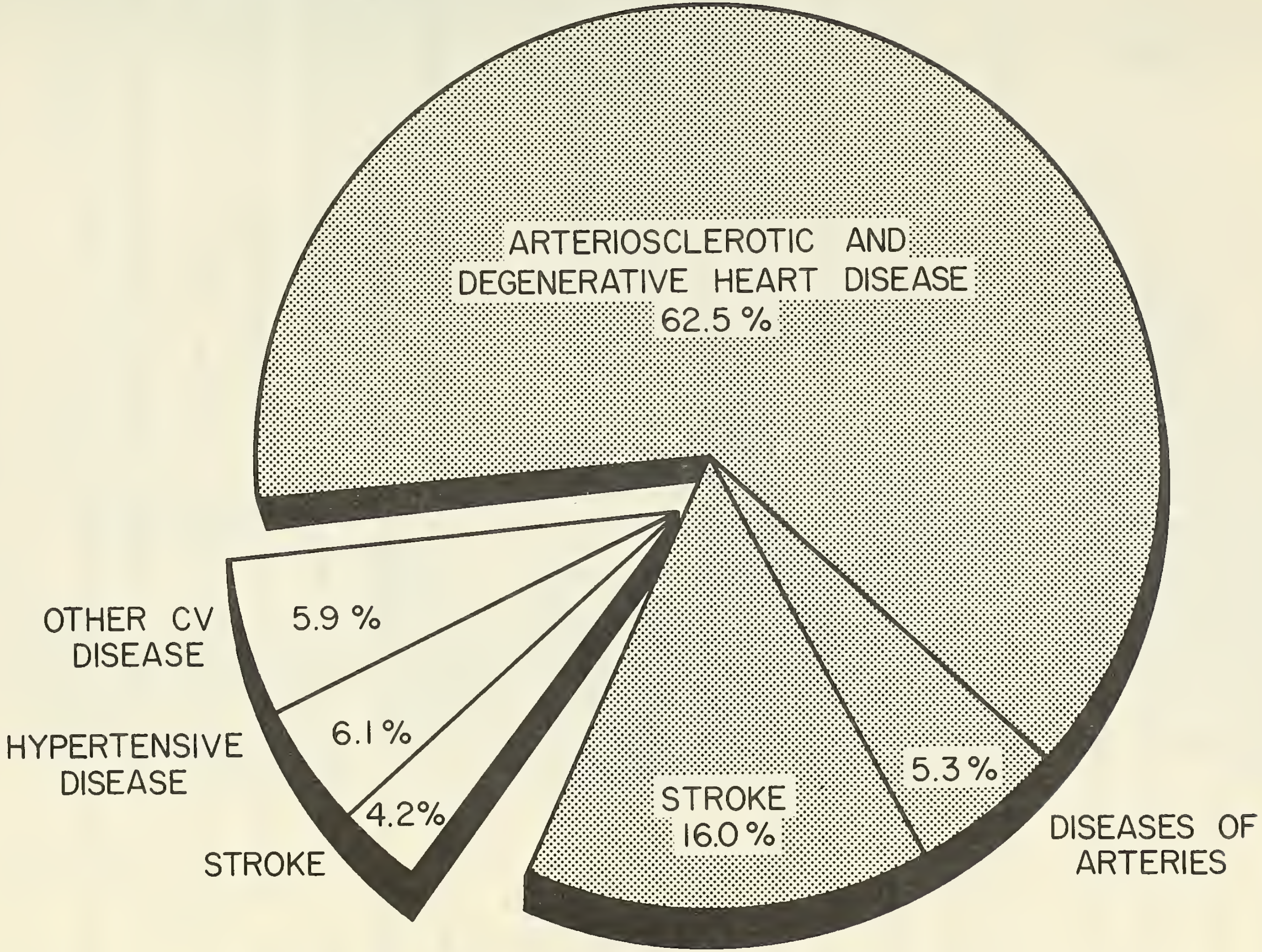


FIGURE 3

Percent Breakdown of Deaths from Cardiovascular Disease by Major Sub-Group and The Proportion Due to Arteriosclerosis*: United States, 1967[2]



is due to hypertension and arteriosclerosis. Thus, over 80 percent of cardiovascular disorders can be ascribed to arteriosclerosis and its complications.

Arteriosclerotic and Degenerative Heart Disease

In 1967, arteriosclerotic and degenerative heart disease accounted for nearly 625,000 deaths (33.8 percent of the total). For the 35 to 64 year age group, the corresponding percentage is 31.1 percent.[2]

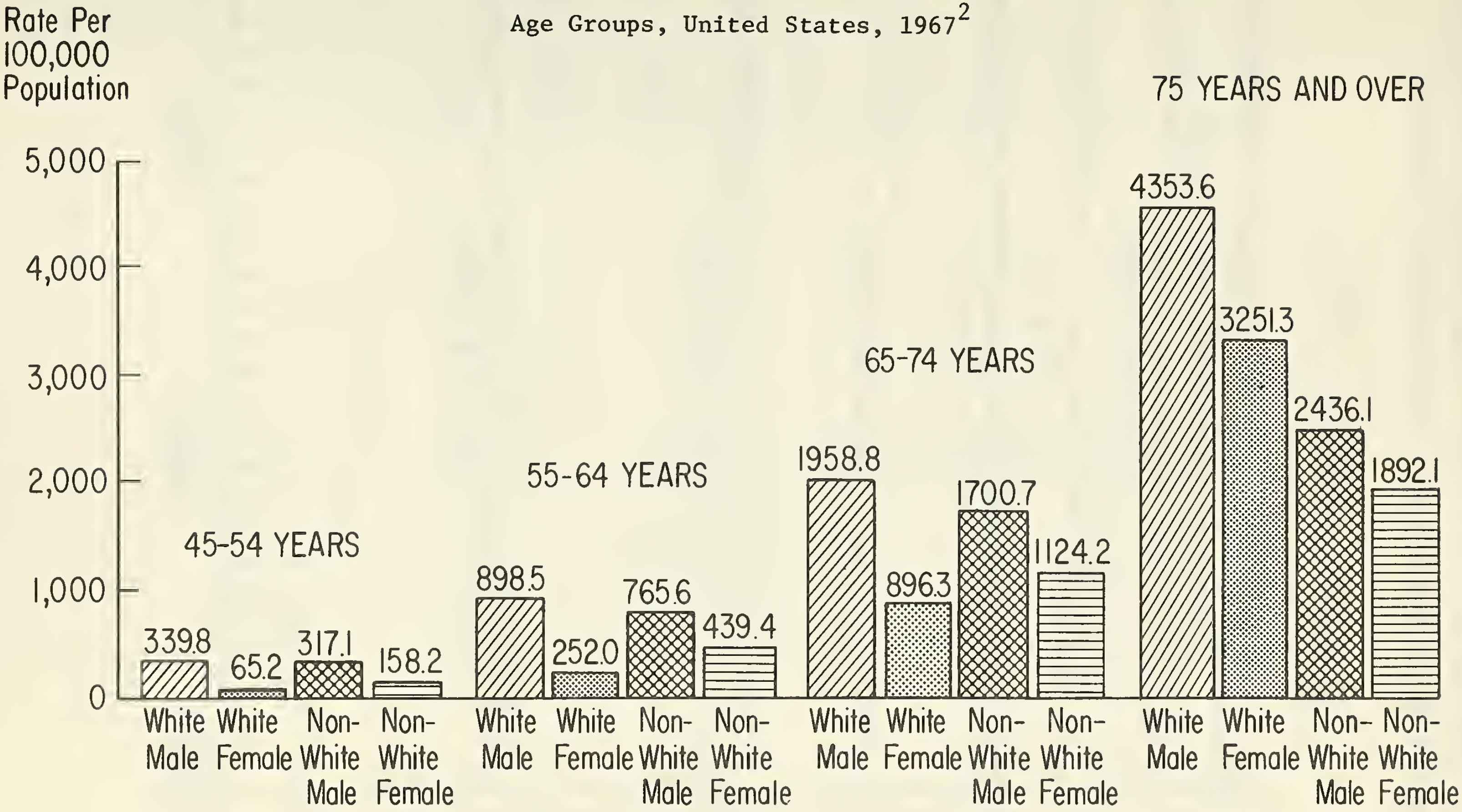
The statistics show a male preponderance in death from this group of diseases and a marked increase in mortality with advancing age (Figure 4). Except for women in the younger age groups, there has been no tendency for the high death rates from arteriosclerotic heart disease to decrease in this country during the past 30 years, despite the significant advances in recognition and treatment of the complications of arteriosclerosis. This unfortunate fact is illustrated in Figures 5 A, B, C, and D. The death rates actually increased from 1940 to 1960, but appear to have leveled off slightly during the last 10 years.

These extremely high death rates from arteriosclerotic heart disease in the United States are not shared by all highly developed nations. As shown in Figure 6,[4] both the total death rate and the death rate from arteriosclerotic heart disease in men aged 45 to 54 years are very high in the United States as compared to Sweden, Switzerland, and Japan. Only Finland suffers more loss of men in this productive age group than does the United States. Figure 7 shows the total mortality and the mortality from arteriosclerosis for men in Sweden and the United States.

An extremely important aspect of arteriosclerotic heart disease is its propensity to cause death so suddenly that effective treatment is impossible,

FIGURE 4

Death Rates for Coronary Heart Disease* by Sex and Color For Selected Age Groups, United States, 1967[2]

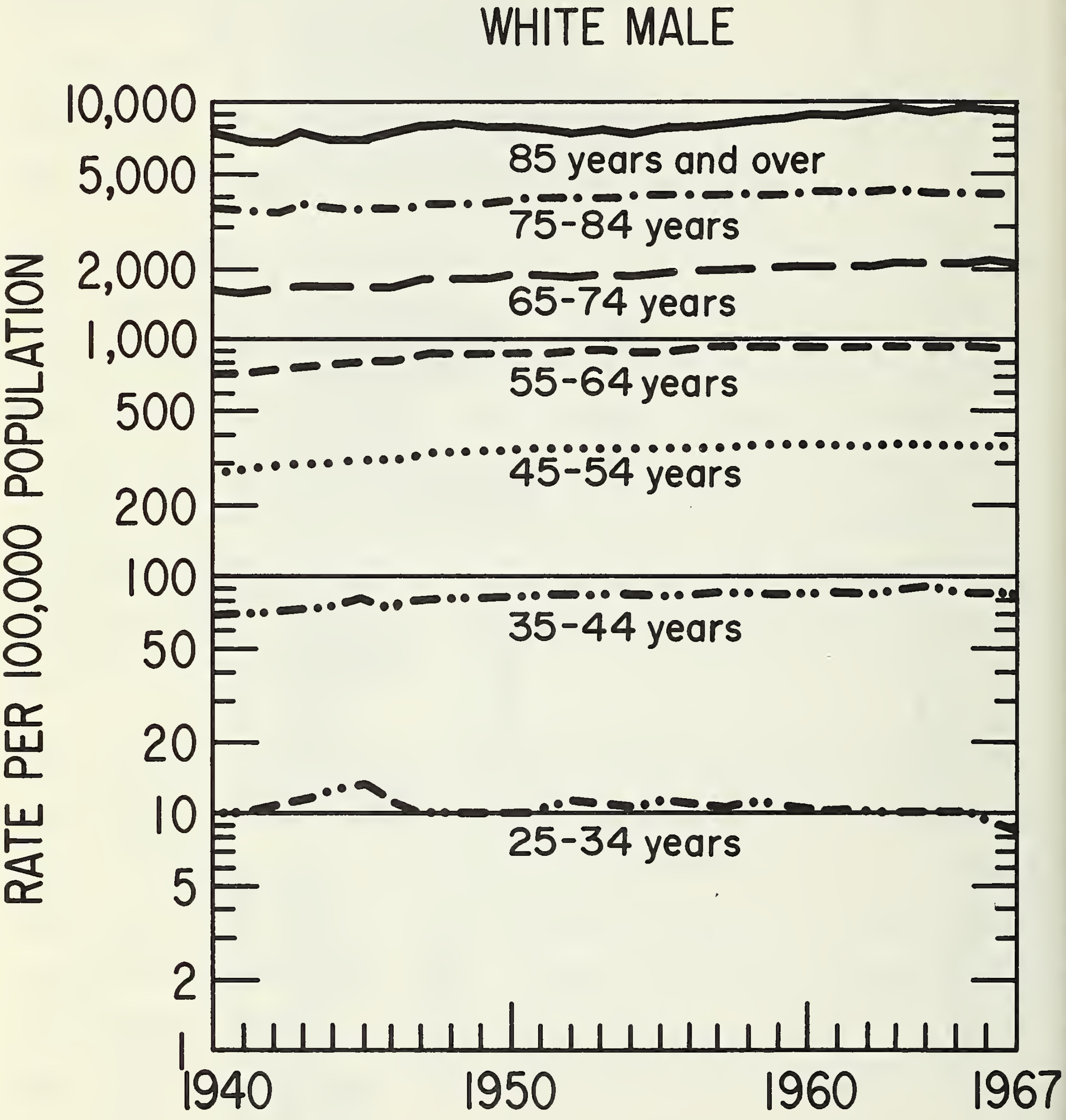


(a) ICD 420

*ICD 420

FIGURE 5A

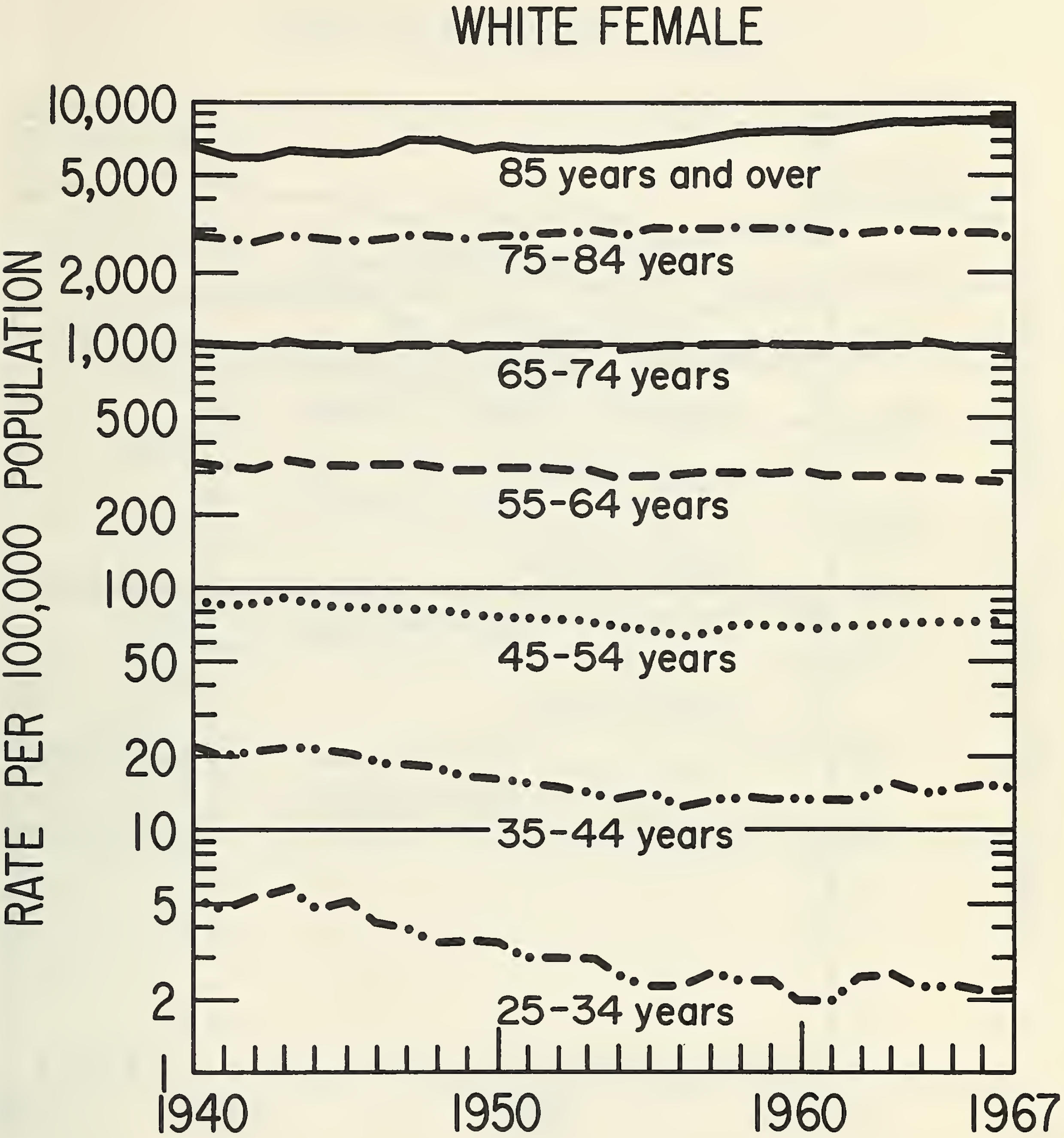
Death Rates for Arteriosclerotic Heart Disease and Myocardial Degeneration* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 420, 422

FIGURE 5B

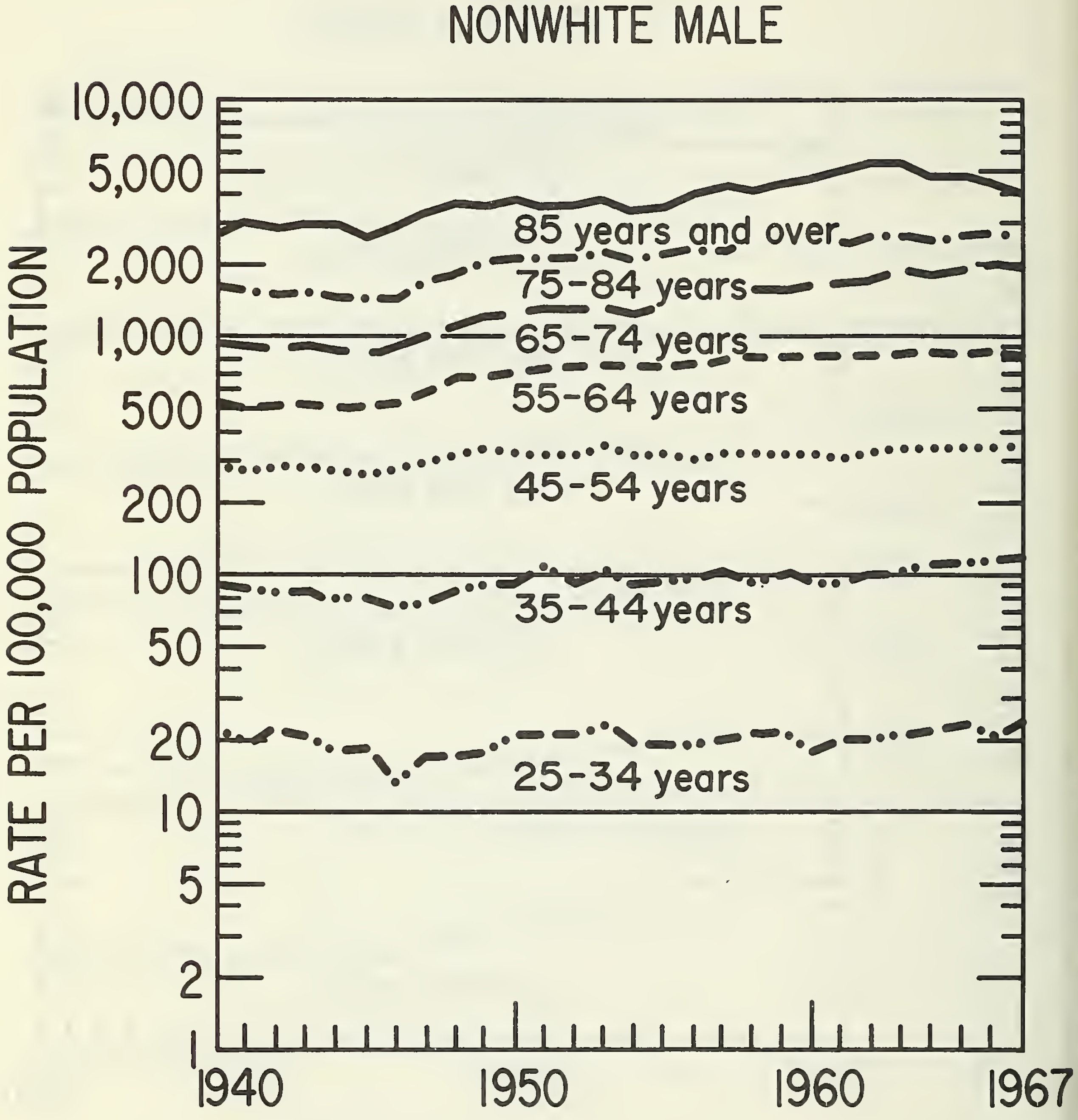
Death Rates for Arteriosclerotic Heart Disease and Myocardial Degeneration* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 420, 422

FIGURE 5C

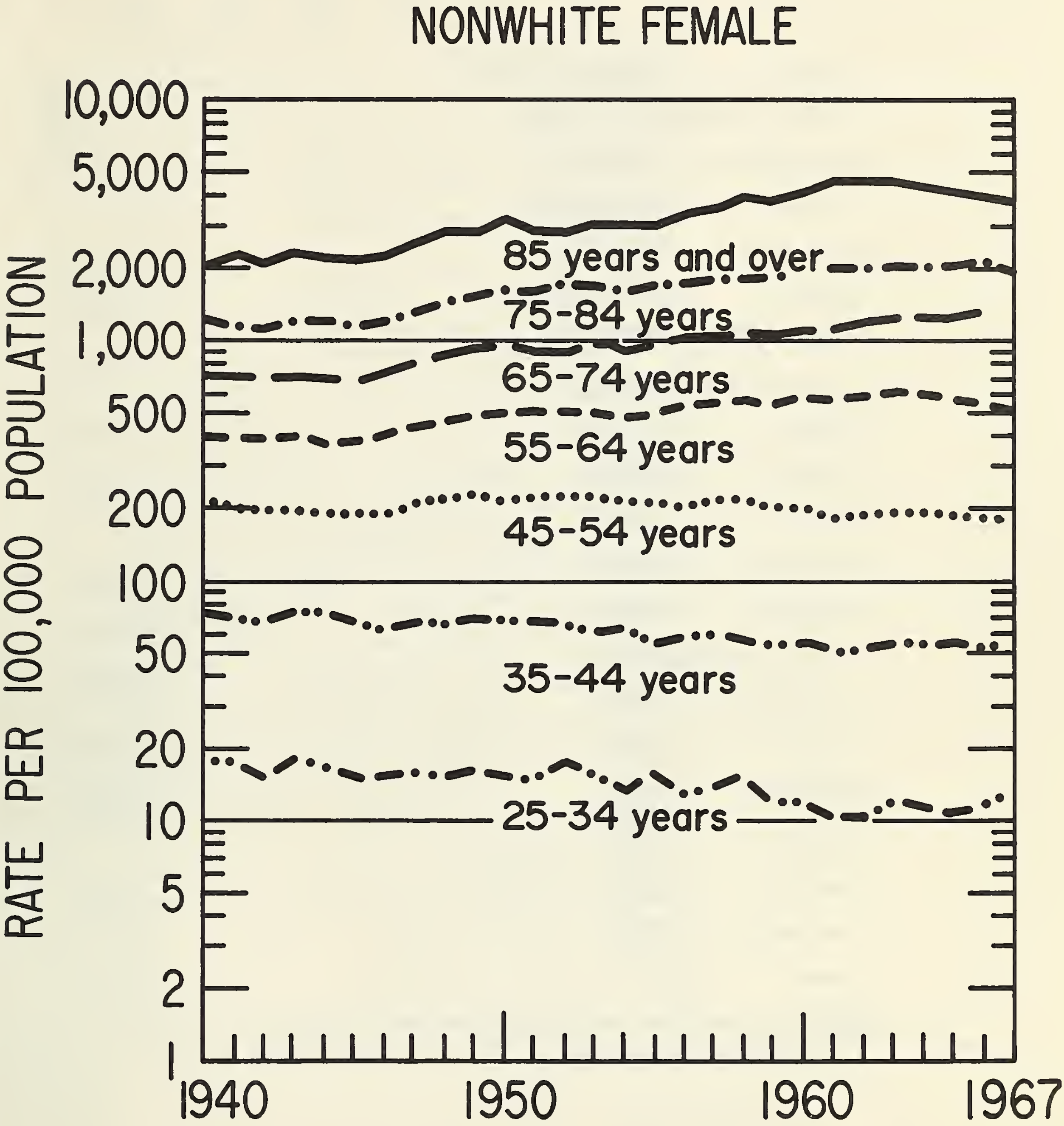
Death Rates for Arteriosclerotic Heart Disease and Myocardial Degeneration* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 420,422

FIGURE 5D

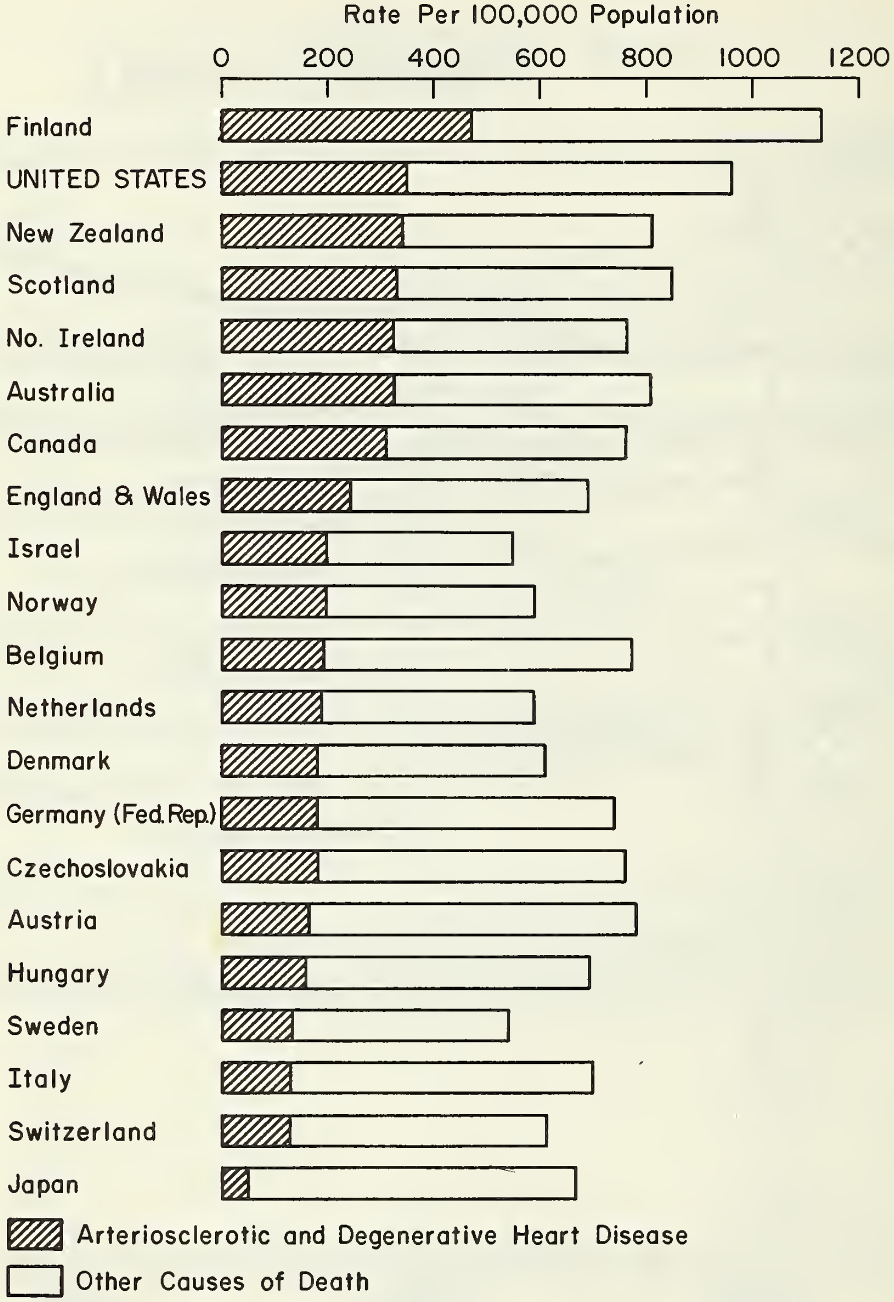
Death Rates for Arteriosclerotic Heart Disease and Myocardial Degeneration* by Sex, for Selected Age Groups, United States, 1940-1967[3]



*ICD 420, 422

FIGURE 6

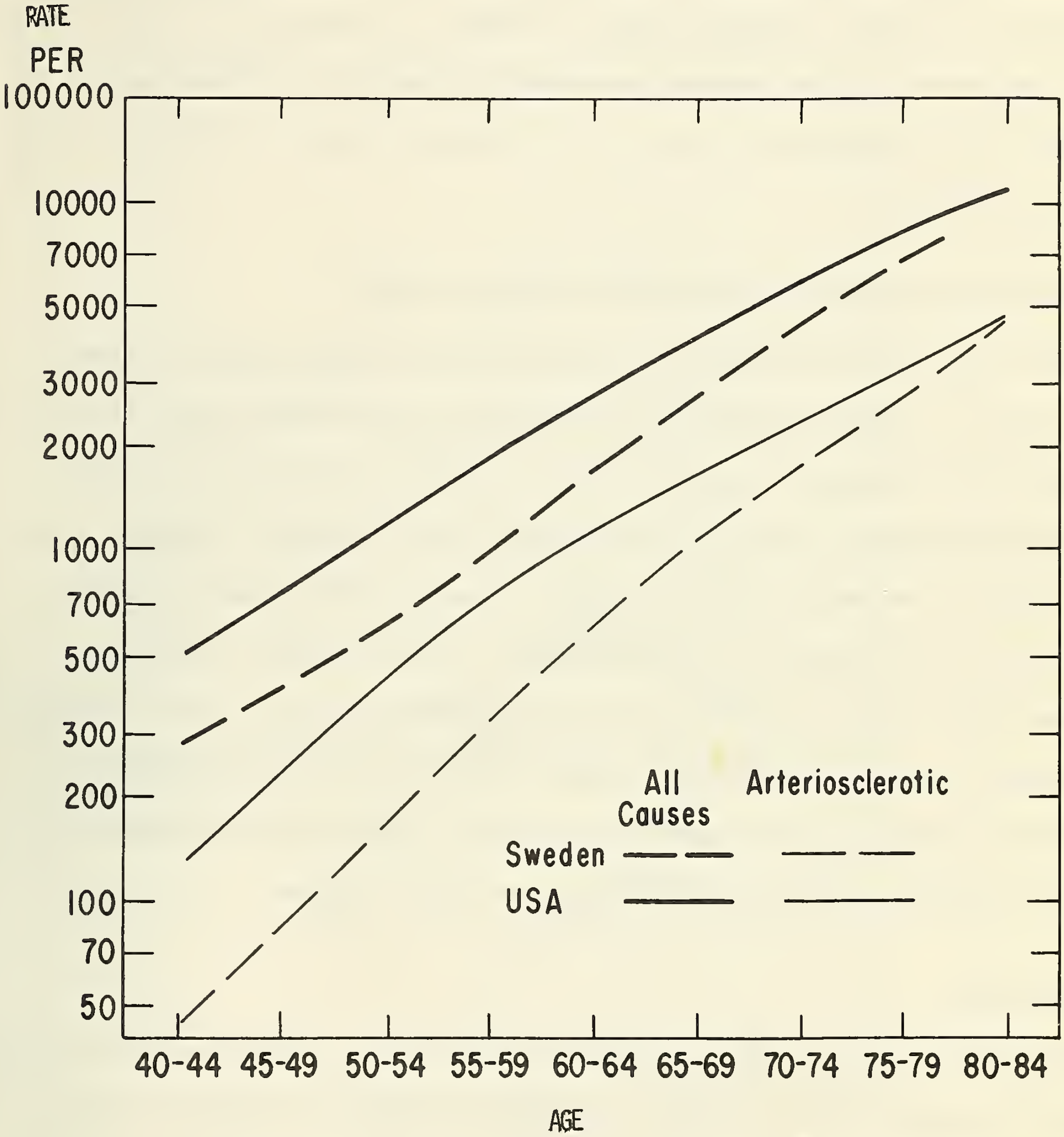
Death Rates from Arteriosclerotic and Degenerative Heart Disease* and from All Causes; Selected Countries, 1967 - Men aged 45-54 years[4]



*ICD 420, 422

FIGURE 7

Total Mortality as Compared with that from Arteriosclerotic and Degenerative Heart Disease for Men in Sweden and the United States 1966



emphasizing the importance of prevention of this disease. In the population study of Framingham, Massachusetts, 65 percent of the coronary heart disease deaths among persons under 65 years of age occurred outside the hospital, the majority suddenly, within one hour of onset of the terminal event.[5] It is known that a high percentage of sudden deaths occur within a matter of minutes. The annual incidence rates of sudden and unexpected coronary deaths as *first* events of this disease are shown in Figure 8 for Framingham men and women.[6] The corresponding rates for all coronary deaths as *first* events are shown in Figure 9.

Vascular Lesions Affecting the Central Nervous System

Stroke is the most common form of disease of the central nervous system. As a cause of death it ranks third, after heart disease and cancer, and is a major cause of disability in the elderly. In 1967, there were more than 200,000 deaths from this cause, accounting for 10.9 percent of deaths from all causes. The death rates from stroke increase markedly with advancing age and, prior to age 75, they are greater in the non-white population (Figure 10).[2] Each of the sex-color groups is experiencing a steady decline in death rates from this disease (Figure 11).[3] This encouraging trend is believed by many to be the result of more effective treatment of hypertension, including more effective treatment of renal diseases.

Hypertension

Statistically, hypertension is difficult to assess as a subgroup of mortality from the cardiovascular diseases. In 1967, hypertension was certified as the underlying cause in more than 61,000 deaths.[2] We know that its role in

FIGURE 8

Average Annual Incidence Rate of Initial Events of Sudden and Unexpected Death from Coronary Heart Disease by Age and Sex Framingham Study, 16-Year Follow-Up[6]

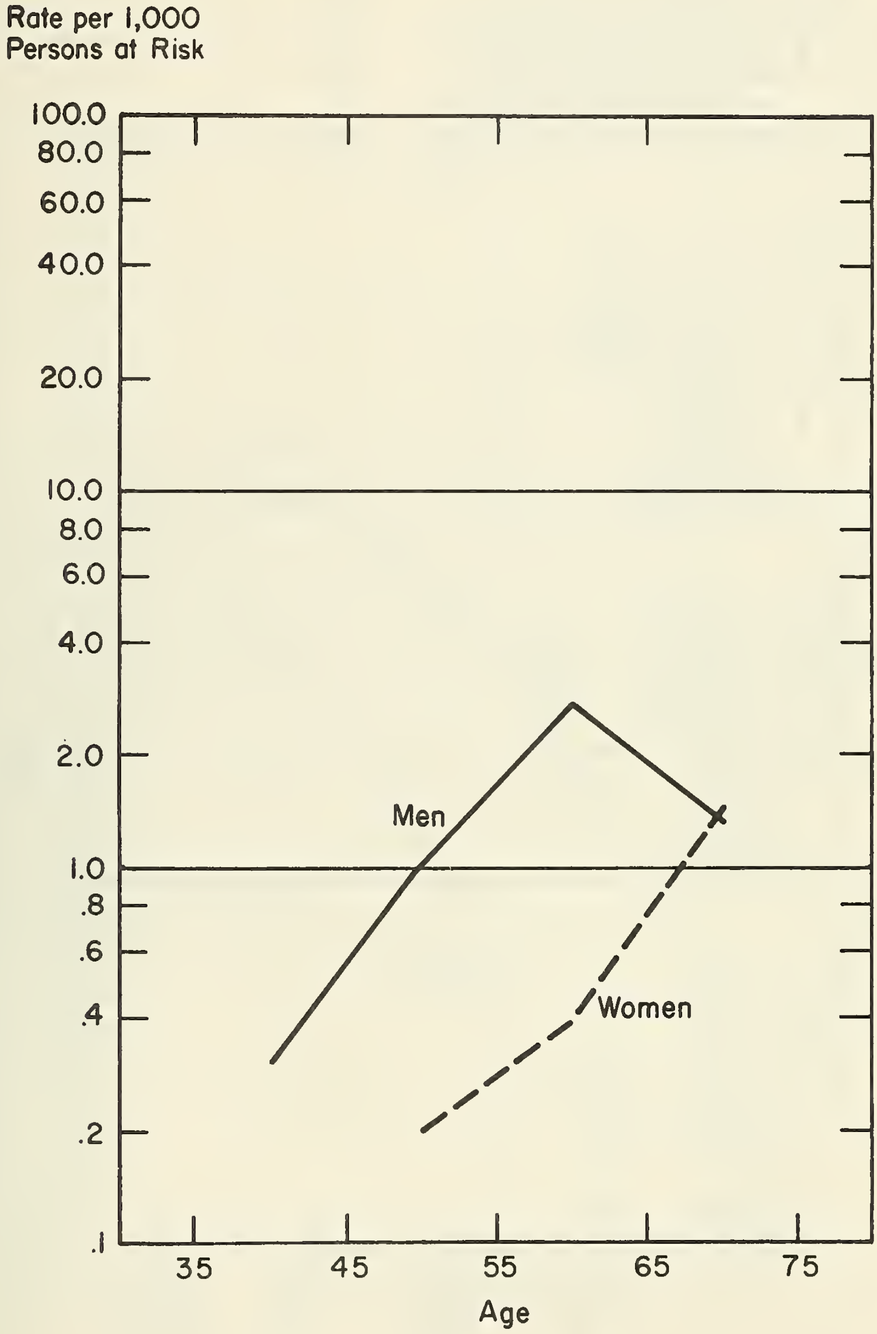


FIGURE 9

Average Annual Incidence Rate of Initial Event of Death from Coronary Heart Disease by Age and Sex, Framingham Study 16 Year Follow-Up[6]

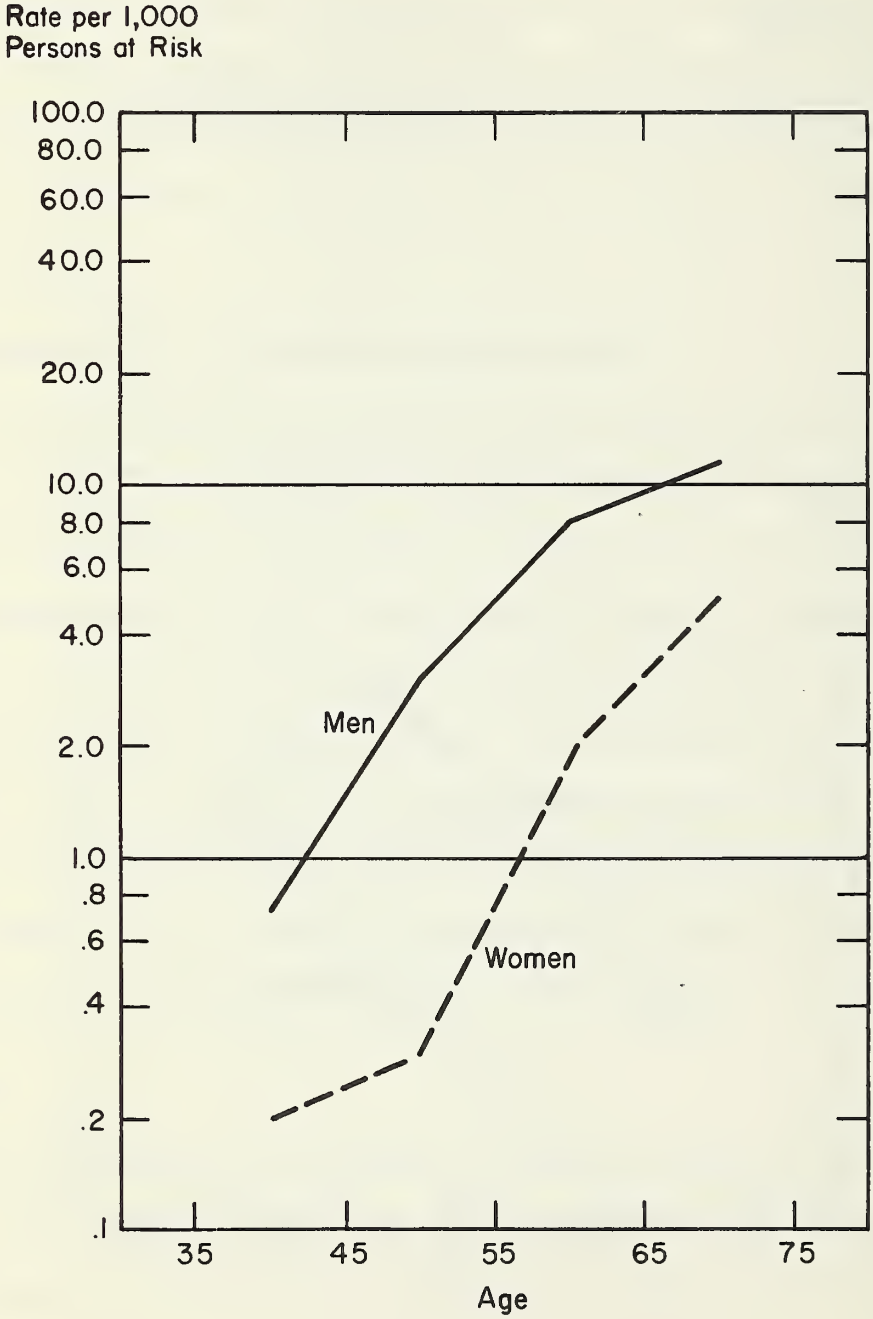
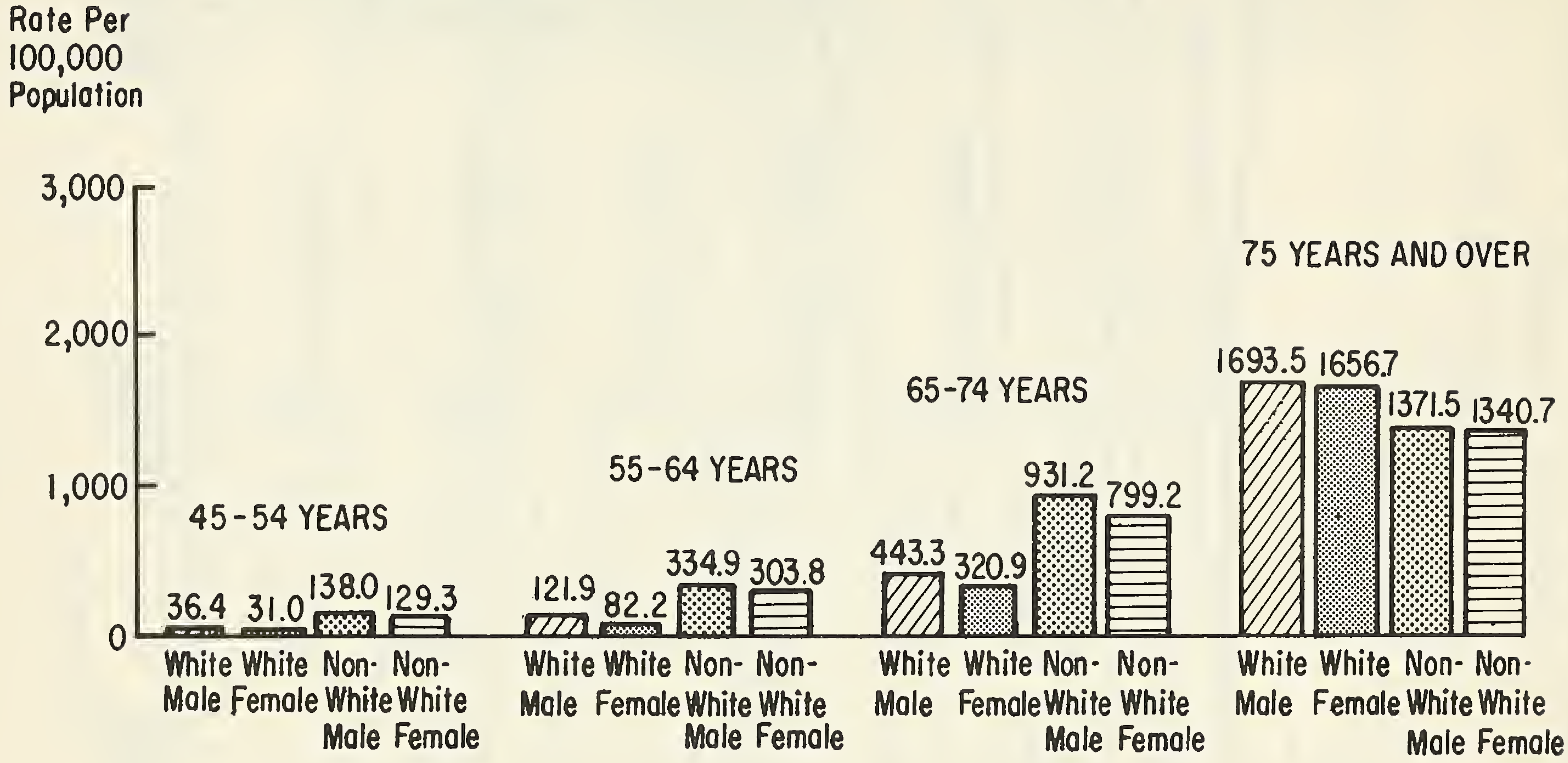


FIGURE 10

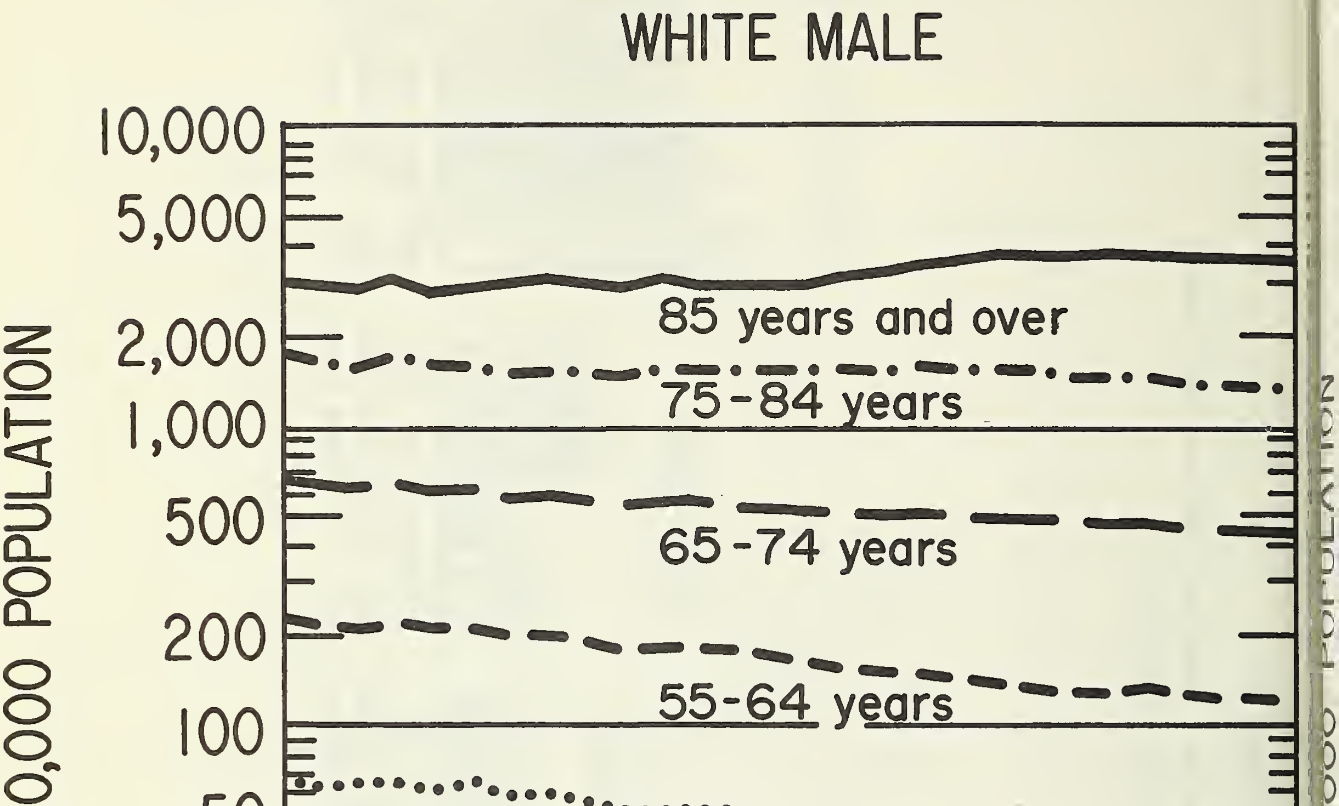
Death Rates for Stroke* By Sex and Color for Selected Age Groups, United States, 1967[2]



*ICD 330-334

FIGURE 11A

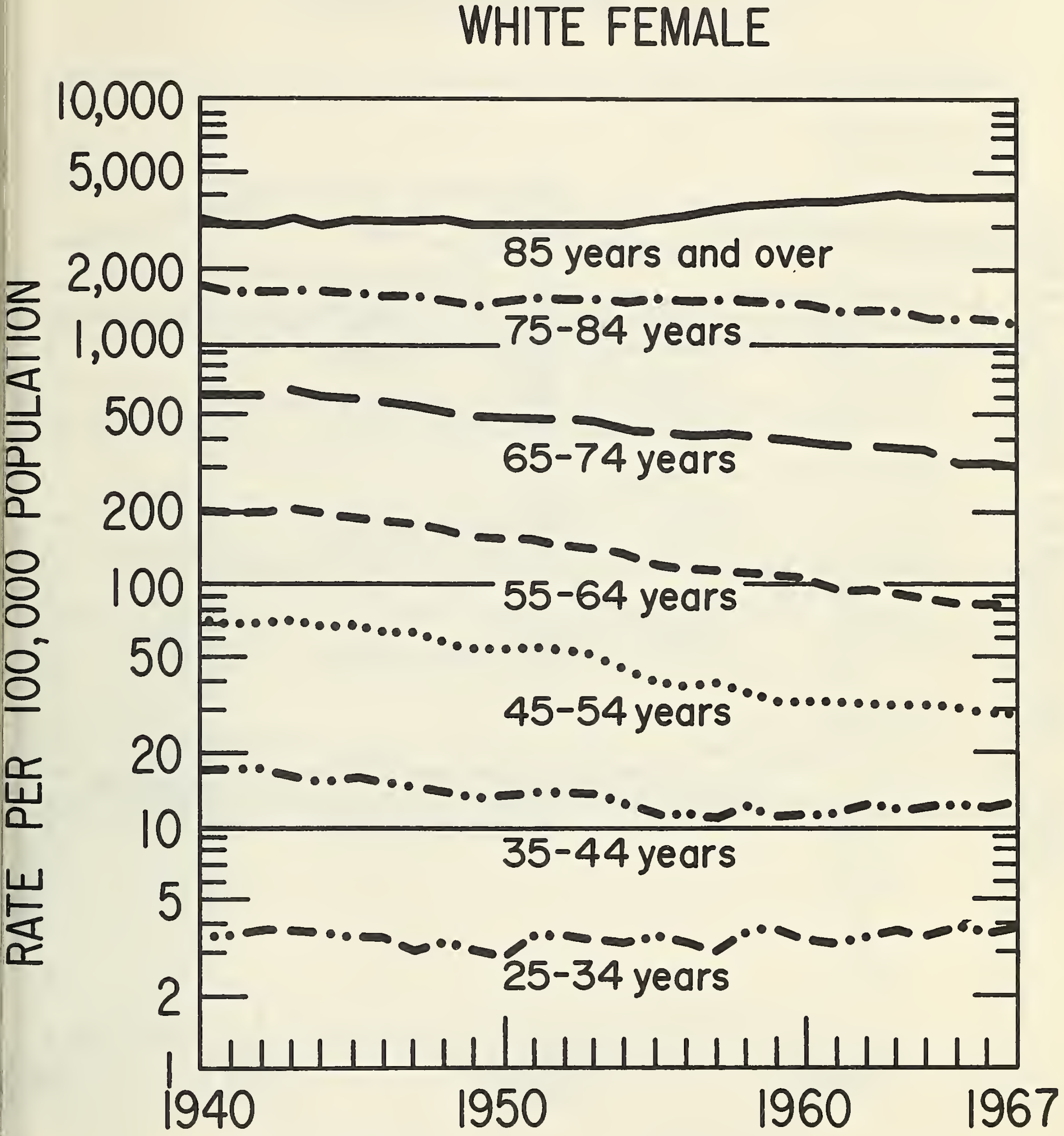
Death Rates for Stroke* by Sex and Selected Age Groups, United States, 1940-1967[3]


WHITE MALE

*ICD 330-334

FIGURE 11B

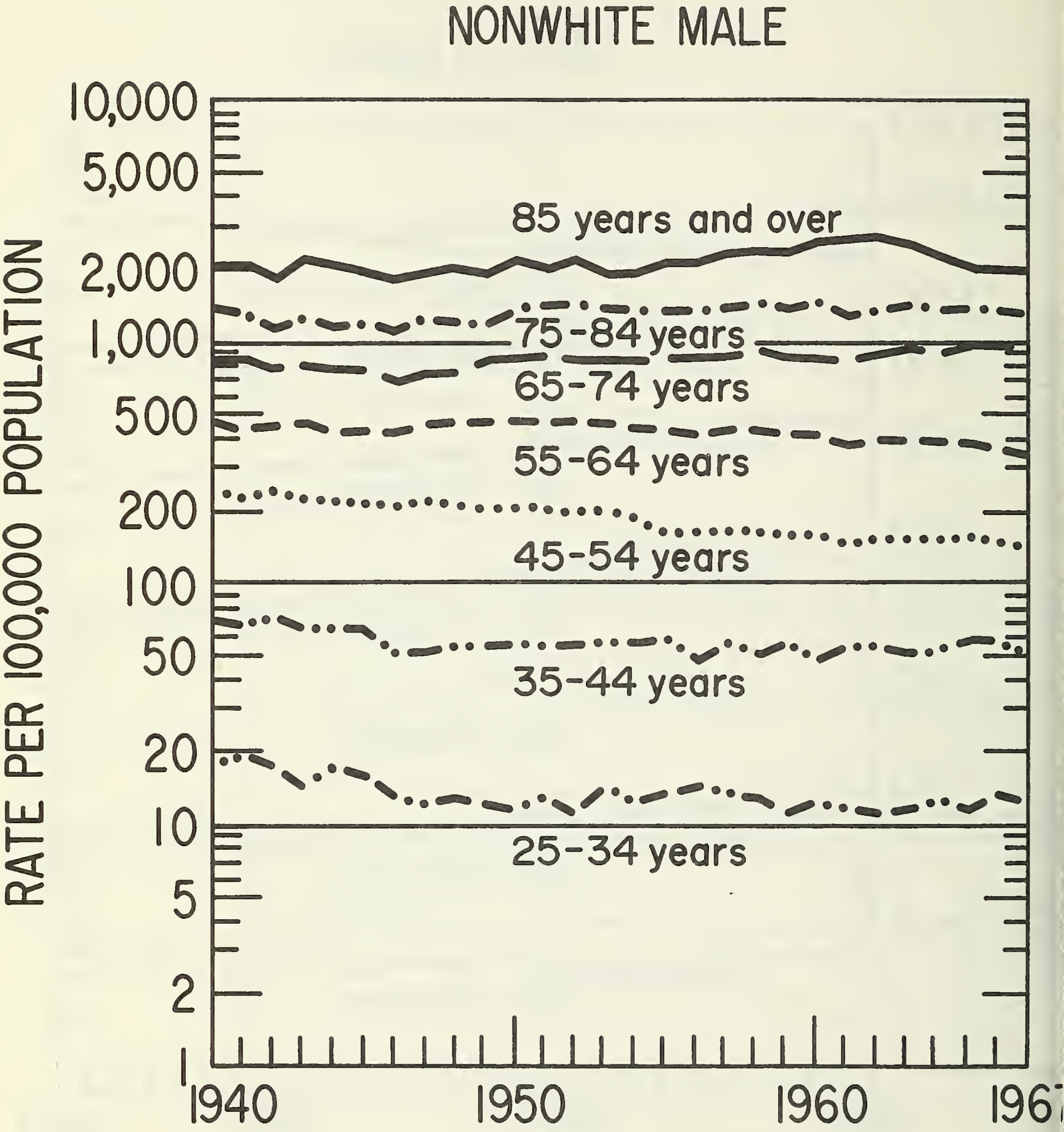
Death Rates for Stroke* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 330-334

FIGURE 11C

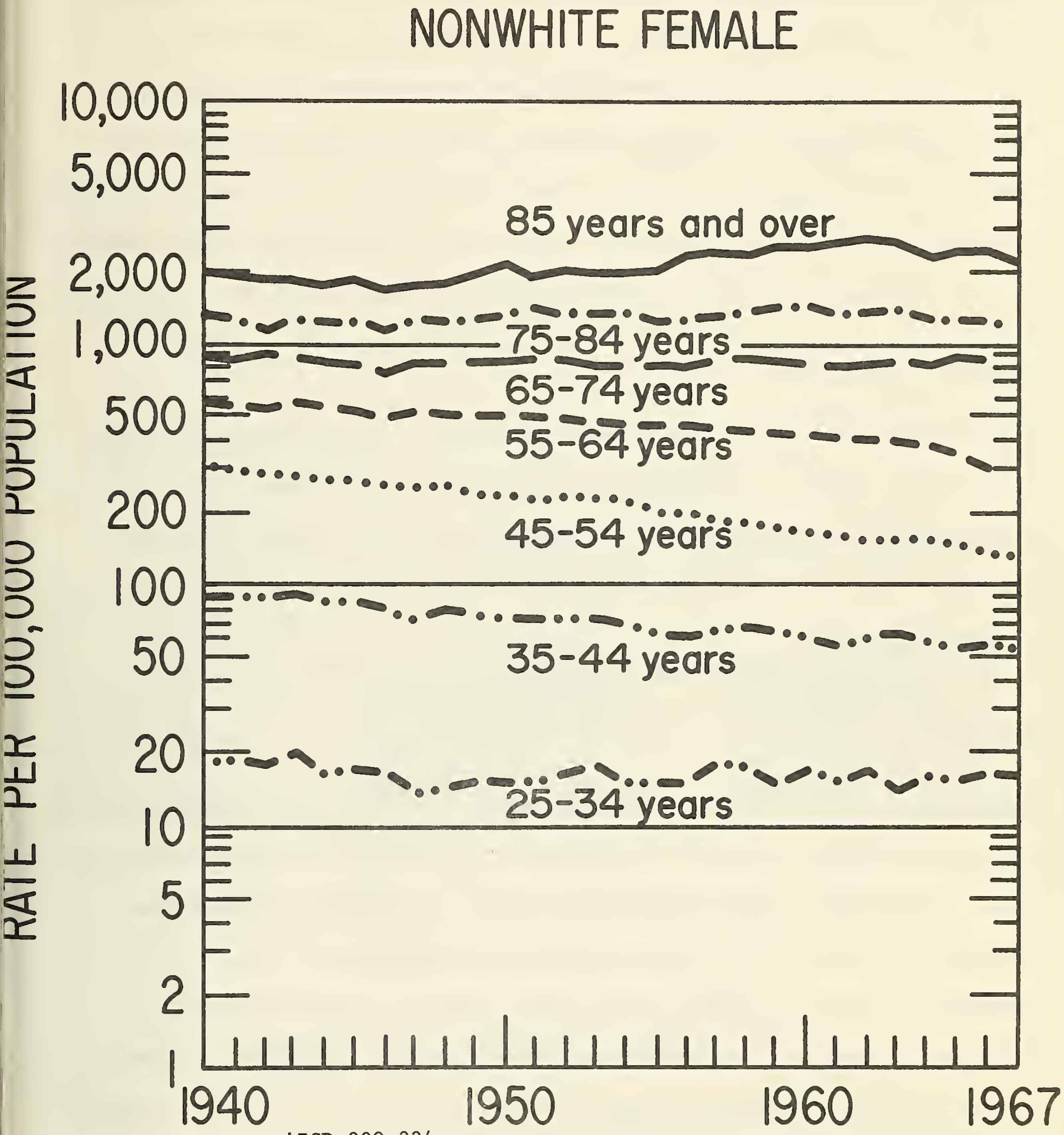
Death Rates for Stroke* by Sex for Selected Age Groups,
United States, 1940-1967[3]



*ICD 330-334

FIGURE 11D

Death Rates for Stroke* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 330-334

death is considerably greater, however, because there is underrecording of hypertension as the underlying cause of death, and there is a coding preference for coronary disease or stroke as the underlying cause when either term is entered on the death certificate with hypertension. Figures 12 and 13 A, B, C, and D reflect only the mortality from hypertension as the underlying cause. The non-white population exhibits a much greater death rate than does the white population, and as in the arteriosclerotic diseases, age is a very significant factor (Figure 12). The trend in death rates from hypertension has been in a marked downward direction (Figures 13A, B, C, and D).

Diseases of Arteries

The mortality statistics from diseases of arteries are difficult to assess as a single subgroup of diseases of the cardiovascular system. Most of the deaths from these causes occur to persons of age 65 or older as shown earlier in Table 1.

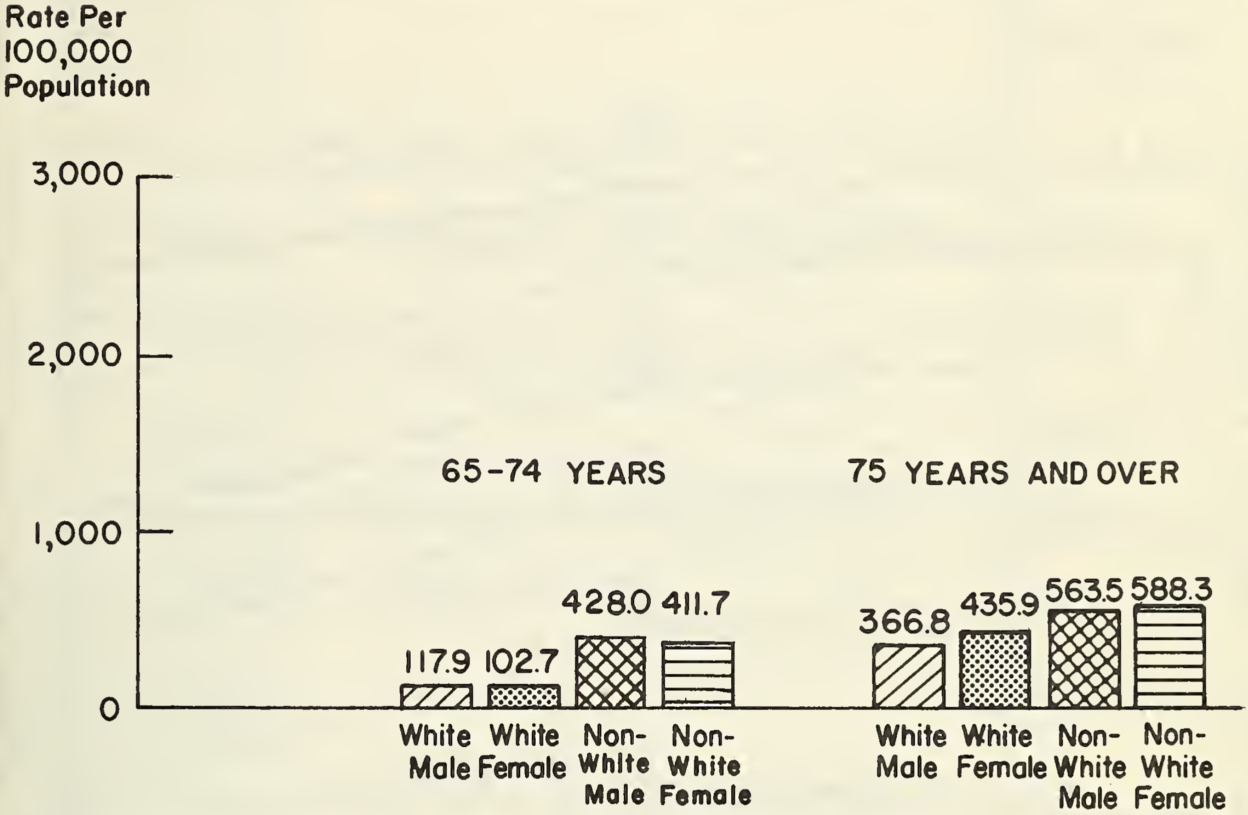
MORBIDITY - ILLNESS AND DISABILITY FROM ARTERIOSCLEROSIS

Prevalence

The clinical manifestations of arteriosclerosis affect a very large proportion of our population as noted by the national and regional surveys on this subject. The National Health Examination Survey of 1960-1962 reported that 5 percent of the civilian, noninstitutionalized population aged 18 to 79 had definite or suspect coronary heart disease based on electrocardiographic evidence of myocardial infarction and the examining physician's impression of the presence or absence of angina pectoris (Table 2).[7] Clinical evidences

FIGURE 12

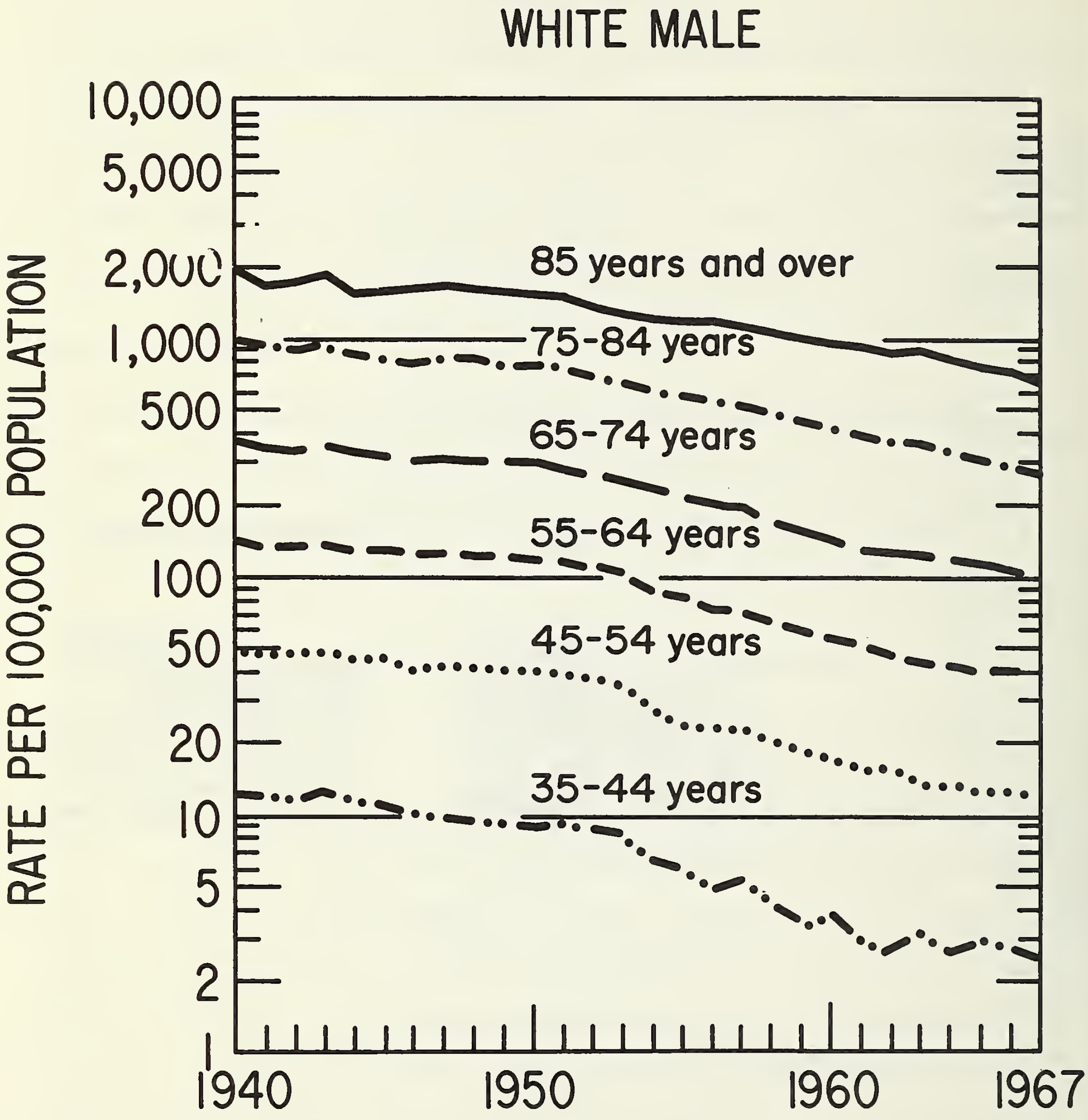
Death Rates for Hypertension and Hypertensive Heart Disease* by Sex and Color for Selected Age Groups, United States, 1967[2]



*ICD 440-447

FIGURE 13A

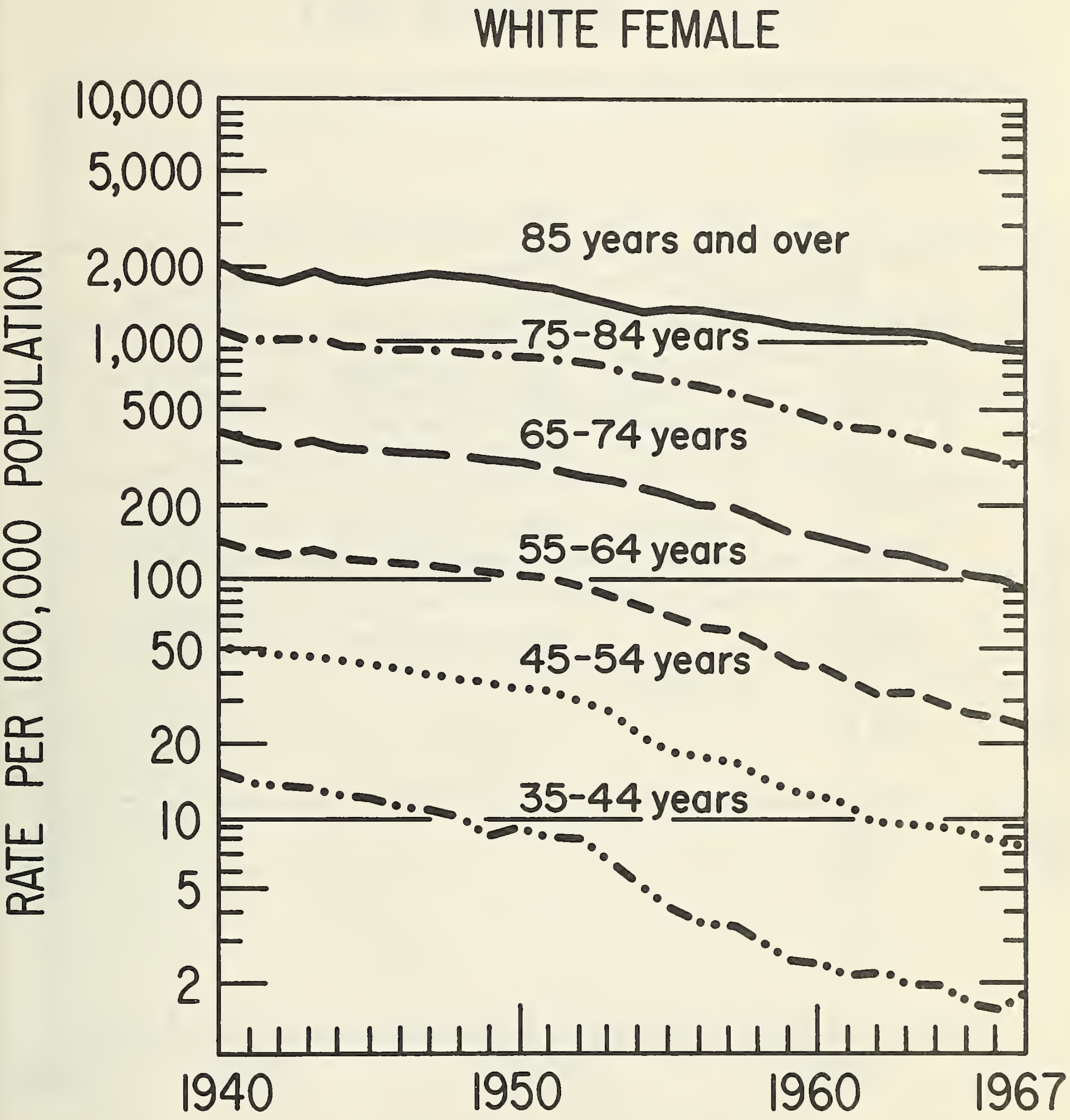
Death Rates for Hypertension* by Sex for Selected Age Groups, United States 1940-1967[3]



*ICD 440-447

FIGURE 13B

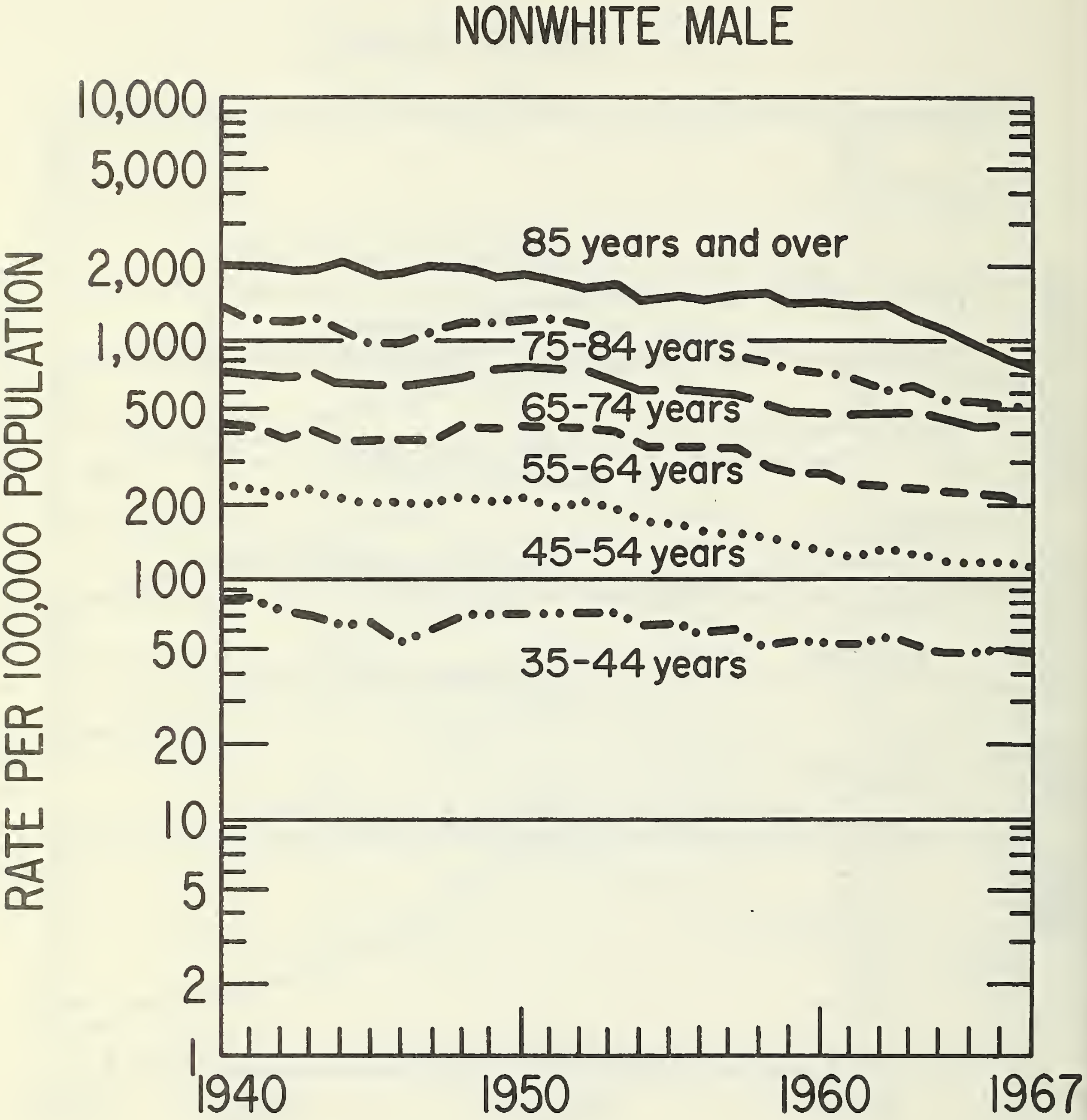
Death Rates for Hypertension* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 440-447

FIGURE 13C

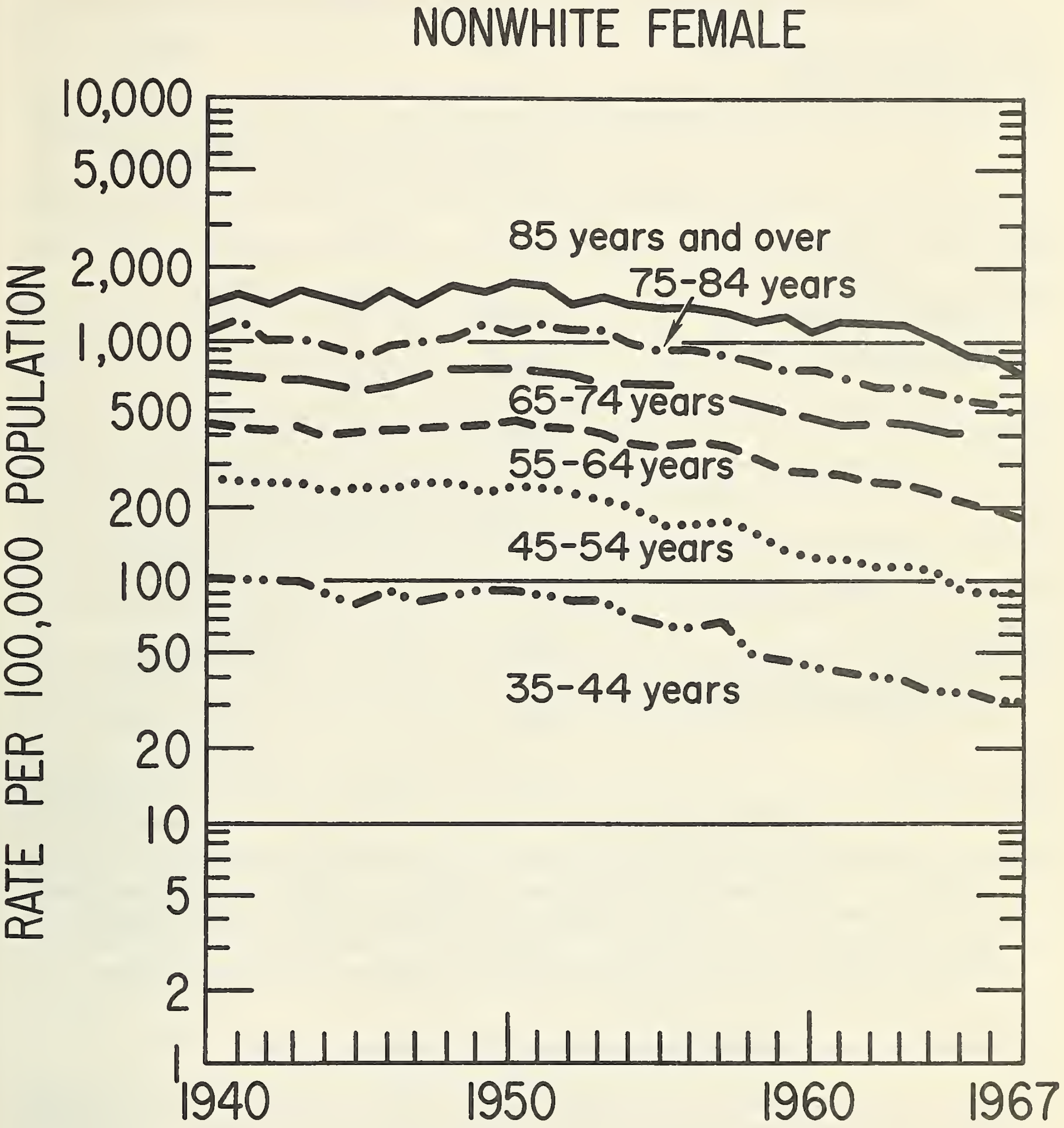
Death Rates for Hypertension* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 440-447

FIGURE 13D

Death Rates for Hypertension* by Sex for Selected Age Groups, United States, 1940-1967[3]



*ICD 440-447

TABLE 2

Number and Percent of the Noninstitutionalized Population Age 18-79 with Coronary Heart Disease, National Health Examination Survey, United States, 1960-1962[7]

Manifestation of Coronary Heart Disease (CHD)	Total	Men	Women
	Number of Persons (in thousands)		
Definite or suspect CHD	5,535	3,081	2,454
Definite CHD (a)	3,125	1,945	1,180
Myocardial infarction (b)	1,421	1,015	406
Angina pectoris or other CHD only	1,704	930	774
Suspect CHD (c)	2,410	1,136	1,274
	Percent of Population		
Definite or suspect CHD	5.0	5.8	4.2
Definite CHD	2.8	3.7	2.0
Myocardial infarction	1.3	1.9	0.7
Angina pectoris or other CHD only	1.5	1.8	1.3
Suspect CHD	2.2	2.2	2.2

(a) One of the following: 1) MI on ECG, definite angina pectoris in the judgment of the examining physician, or both. Angina pectoris was not ascribed to coronary heart disease if aortic stenosis or syphilitic heart disease was present; 2) History of MI in the judgment of the examining physician and an ECG manifesting either left ventricular ischemia or outside criteria.

(b) On ECG with or without angina pectoris or history of MI.

(c) One of the following: 1) History of MI in the judgment of the examining physician with no evidence of MI or left ventricular ischemia on the ECG; 2) Suspect angina pectoris in the judgment of the examining physician.

Note: All categories are exclusive, in descending priority.

of arteriosclerotic heart disease were present in 1.6 percent of persons 35 to 44 years of age, 5.5 percent of persons 45 to 54 and 11.9 percent of persons in the 55 to 64 year age group. The prevalence rates of definite myocardial infarction are shown in Figure 14 by age for men and women.

The survey also reported that 15 percent of the population had definite hypertension and another 15 percent had borderline hypertension (Table 3).[8] The percentage of young persons with definite hypertension is significant; 10.9 percent for persons 35 to 44 years of age, 18.2 percent for persons aged 45 to 54, and 26.9 percent for persons in the 55 to 64 year age group. An analysis of the prevalence rates, Figure 15, shows that Negroes experience higher rates at all ages as compared to whites in the population surveyed.

The number of Americans who had had a stroke was almost 1.7 million in 1967; one-third were under 65 years of age.[9] According to estimates from the National Health Interview Survey, 1.5 million in the noninstitutionalized population had had a stroke. Another 200,000 stroke victims were residents or patients of the nation's 17,400 nursing and personal care homes.[10]

Incidence

Estimates of incidence, that is, the number of events of these diseases occurring in a one-year period, are available for the Framingham, Massachusetts study. A national study of incidence of arteriosclerotic events has not been conducted. The Framingham criteria of the events for which incidence rates are shown are given at the end of this appendix.

The incidence rates of initial events of coronary heart disease (Figure 16)

FIGURE 14

Percent of Adults with Definite Myocardial Infarction, by Age and Sex, United States, 1960-62[7]

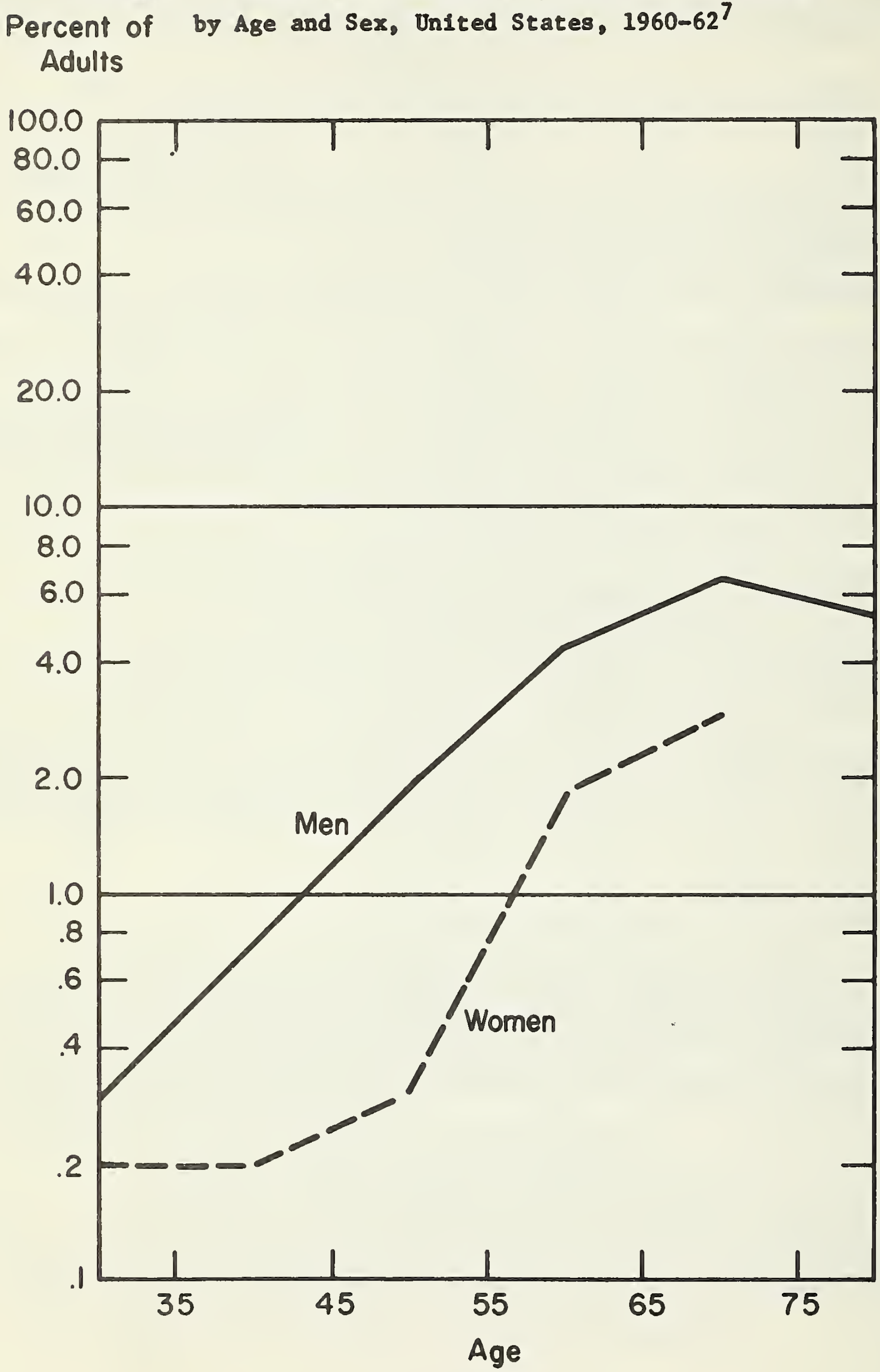


TABLE 3

Number and Percent of the Civilian, Noninstitutionalized Population Age 18-79 With Hypertension, United States, 1960 - 1962[8]

Hypertension	Total	White Men	White Women	Negro Men	Negro Women
	Number of Persons (in thousands)				
Definite or Borderline	33,190	14,189	14,170	2,161	2,353
Definite (a)	17,008	5,949	7,852	1,388	1,656
Borderline (b)	16,182	8,240	6,318	773	697
	Percent of Population				
Definite or Borderline	29.9	30.5	27.5	41.6	37.8
Definite	15.3	12.8	15.3	26.7	26.6
Borderline	14.6	17.7	12.3	14.9	11.2

(a) Blood pressure of 160 mm. Hg. or over systolic, 95 mm. Hg. or over diastolic.

(b) Below 160 mm. Hg. systolic and below 95 mm. Hg. diastolic, but not simultaneously below both 140 mm. Hg. systolic and 90 mm. Hg. diastolic.

FIGURE 15

Percent of Adults with Definite Hypertension, by Age, Race, and Sex United States, 1960-62[8]

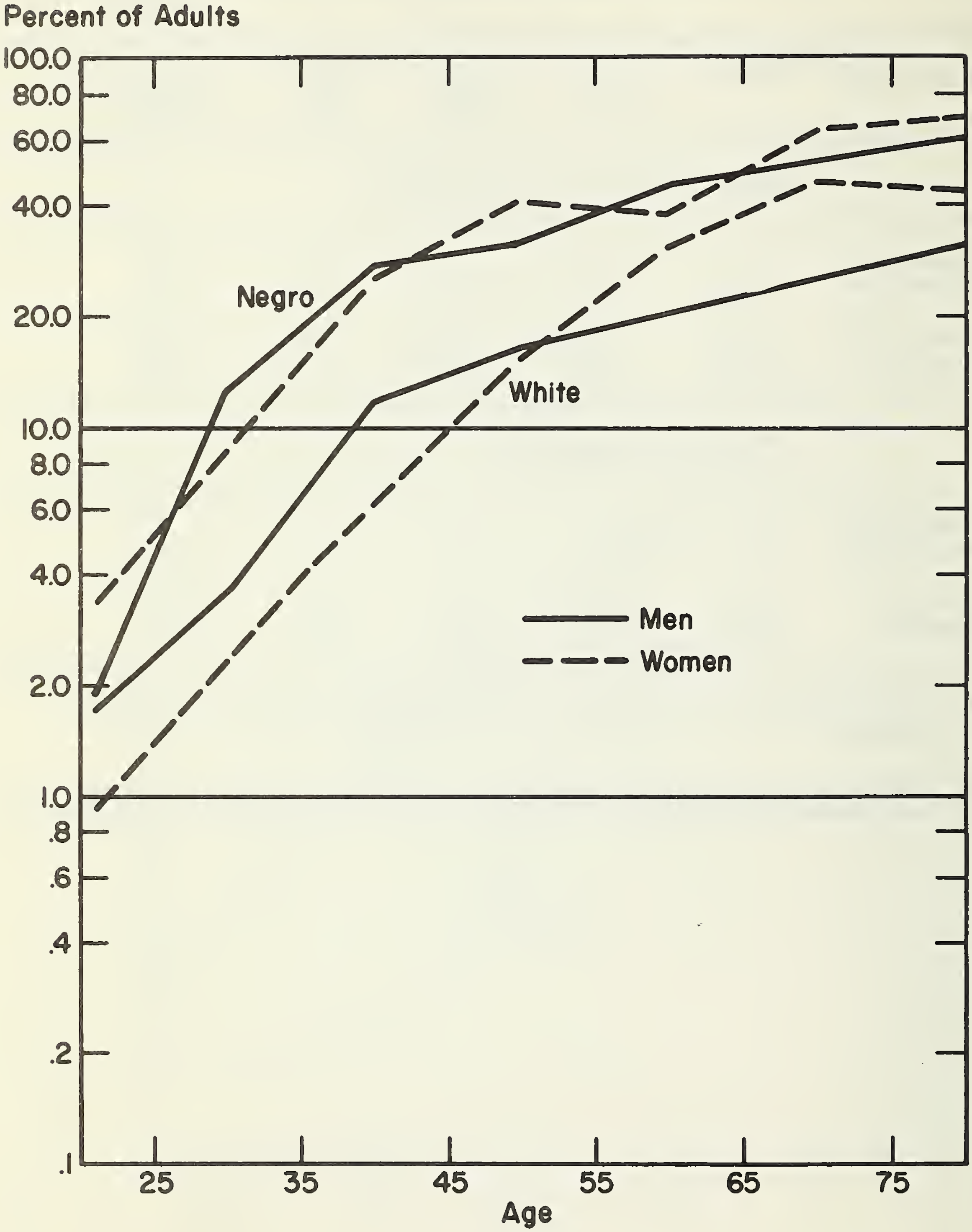
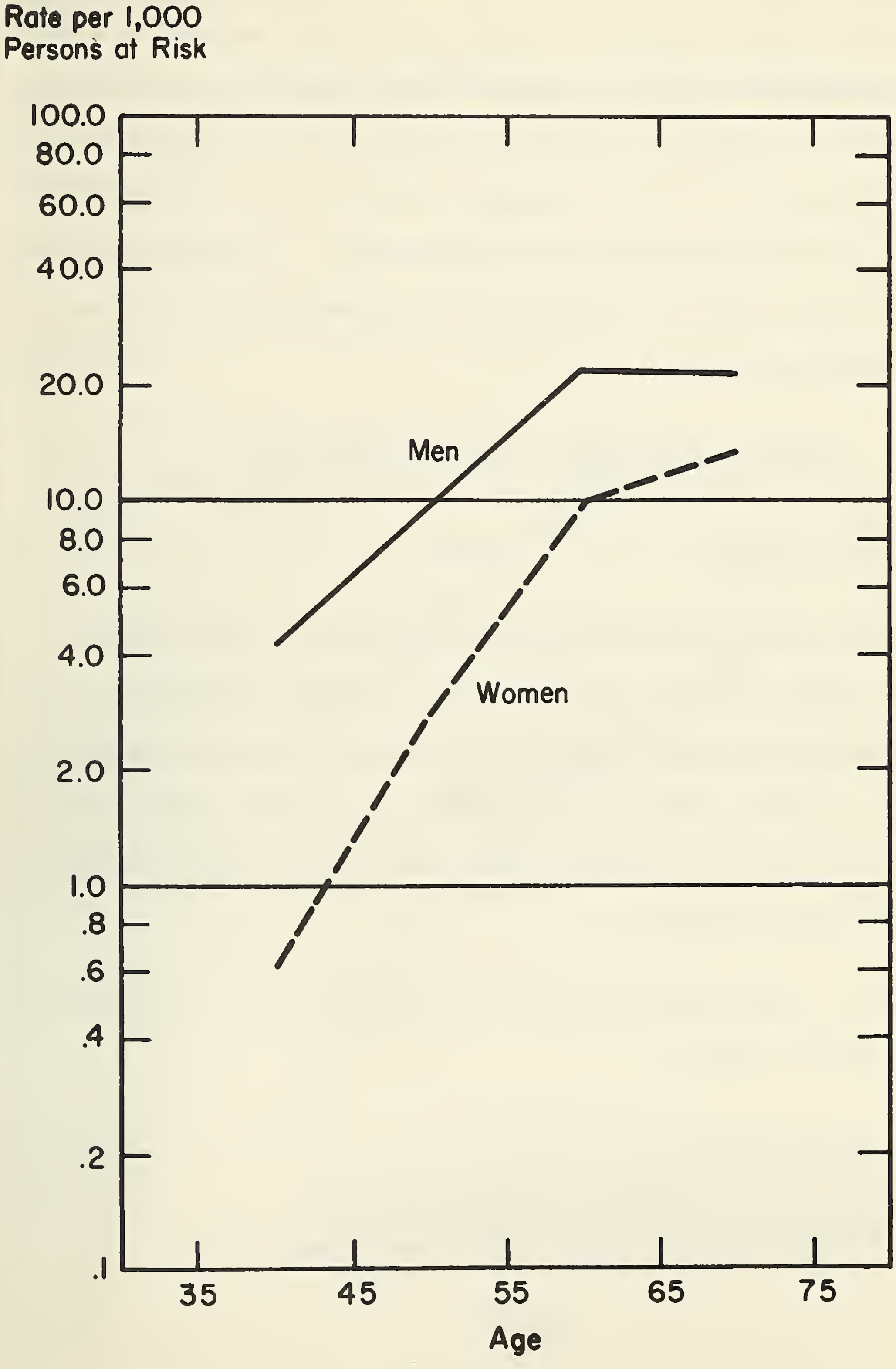


FIGURE 16

Average Annual Incidence Rate of Initial Events of Coronary Heart Disease by Age and Sex, Framingham Study, 16-Year Follow-Up[6]



reflect the preponderance of the disease in older persons and in men. If it is assumed that these rates are representative of the entire population of the nation aged 35 to 74 years, then approximately 650,000 initial events of this disease occur each year among the population of this age group. The corresponding Framingham incidence rates of initial events of myocardial infarction are given in Figure 17, of stroke in Figure 18, and intermittent claudication in Figure 19. If it is assumed that these rates exist in the nation's 35-74 year-old population, then approximately 175,000 strokes and about 150,000 initial events of intermittent claudication would occur each year in this population group.

CRITERIA FOR EVENTS: THE FRAMINGHAM STUDY

1. Coronary Heart Disease

A subject in the study was diagnosed as having developed coronary heart disease (CHD) if upon review of the case a panel of investigators agreed on a definite manifestation of CHD: myocardial infarction, coronary insufficiency, angina pectoris, sudden death from CHD, or non-sudden death from CHD. Persons with preexisting CHD at Exam 1 were excluded from the population at risk of developing CHD.

Preexisting CHD. Preexisting CHD at Exam 1 was identified by any one of the following diagnoses at Exam 1:

Definite angina pectoris
Definite history of myocardial infarction
Definite myocardial infarction by electrocardiogram
Doubtful myocardial infarction by electrocardiogram
Definite coronary insufficiency by electrocardiogram

FIGURE 17

Average Annual Incidence Rate of Initial Events of Myocardial Infarction by Age and Sex, Framingham Study, 16-Year Follow-Up[6]

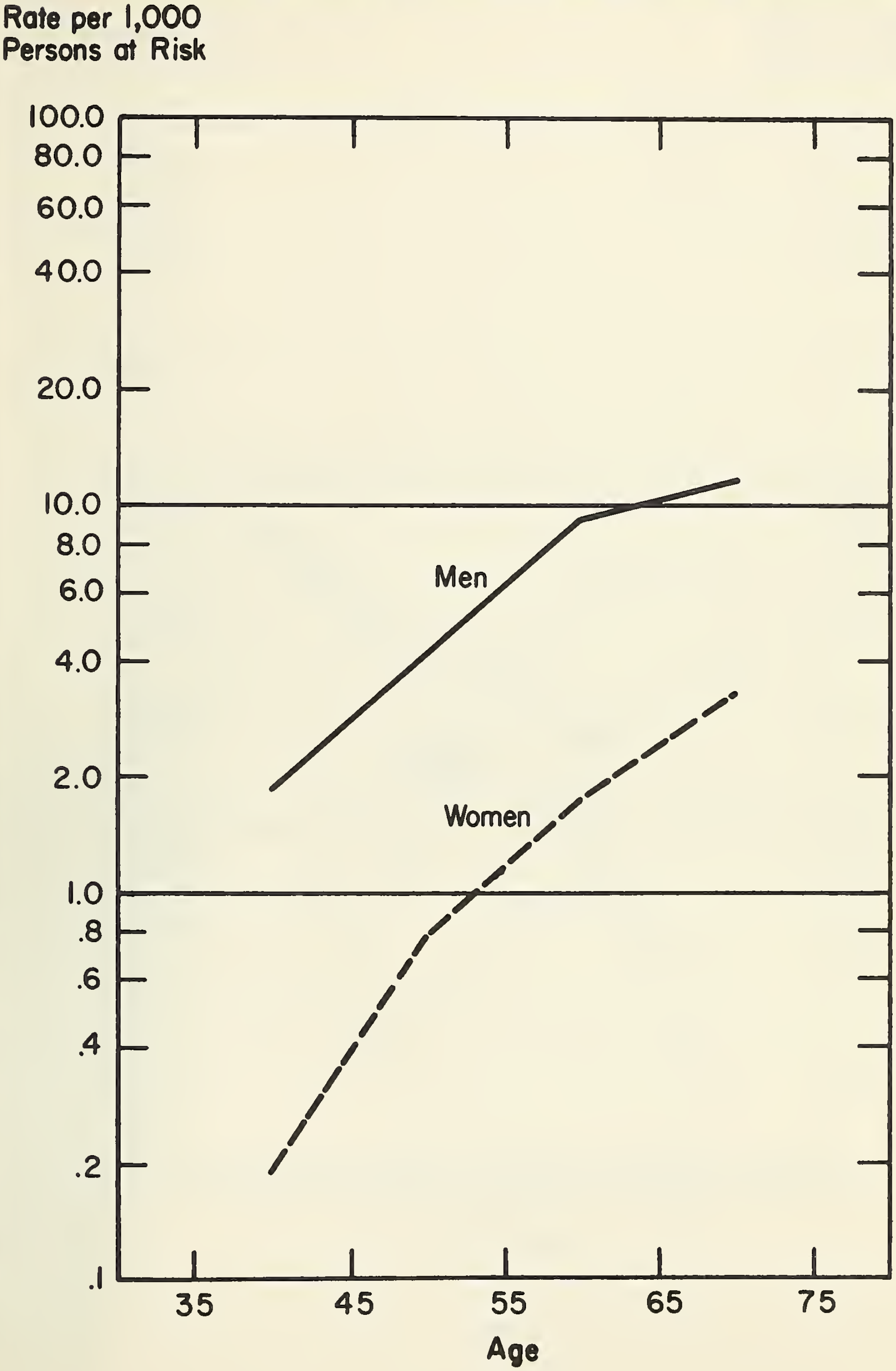


FIGURE 18

Average Annual Incidence Rate of Initial Events of Cerebrovascular Accidents by Age and Sex, Framingham Study, 16-Year Follow-Up[6]

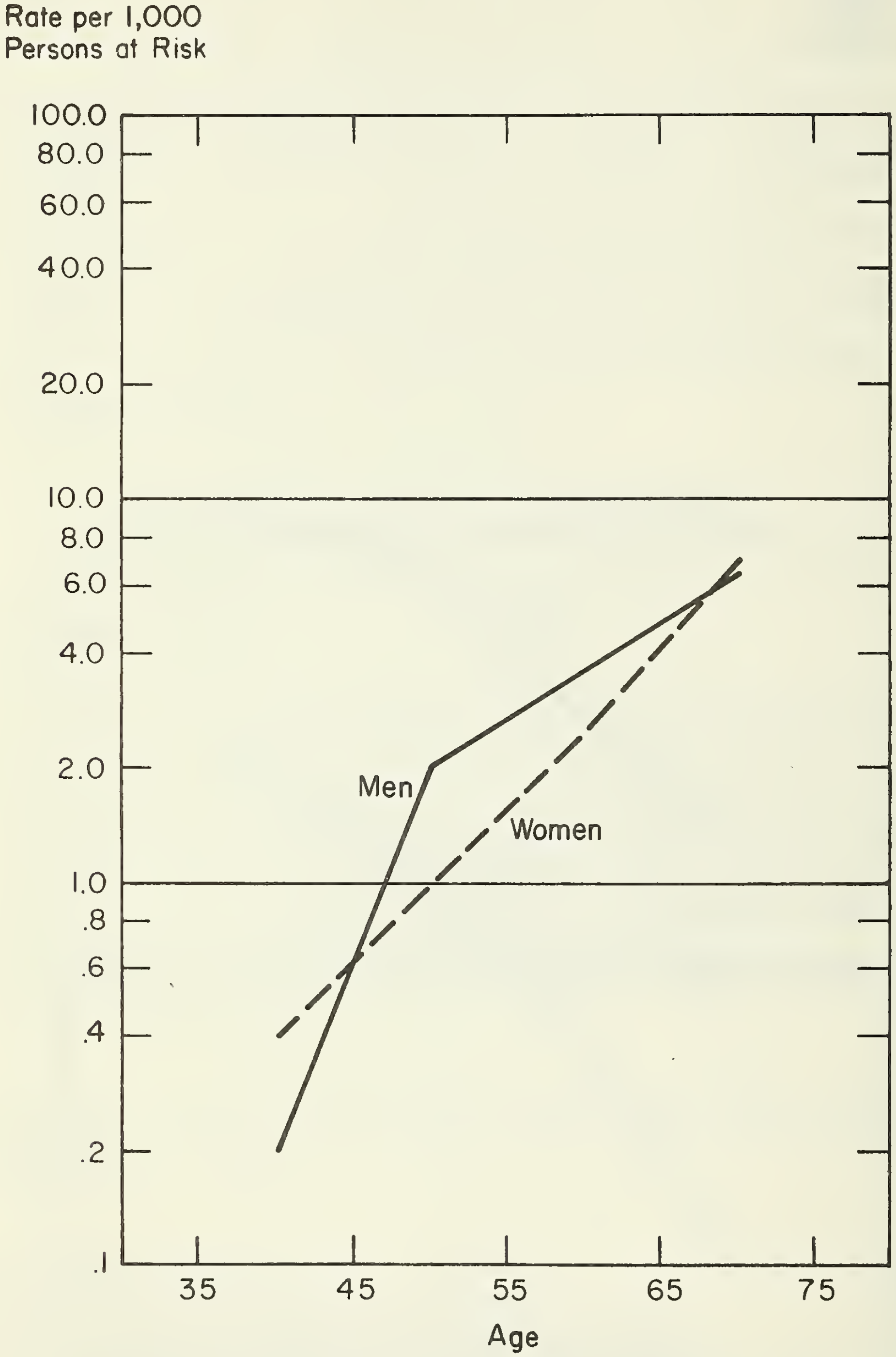
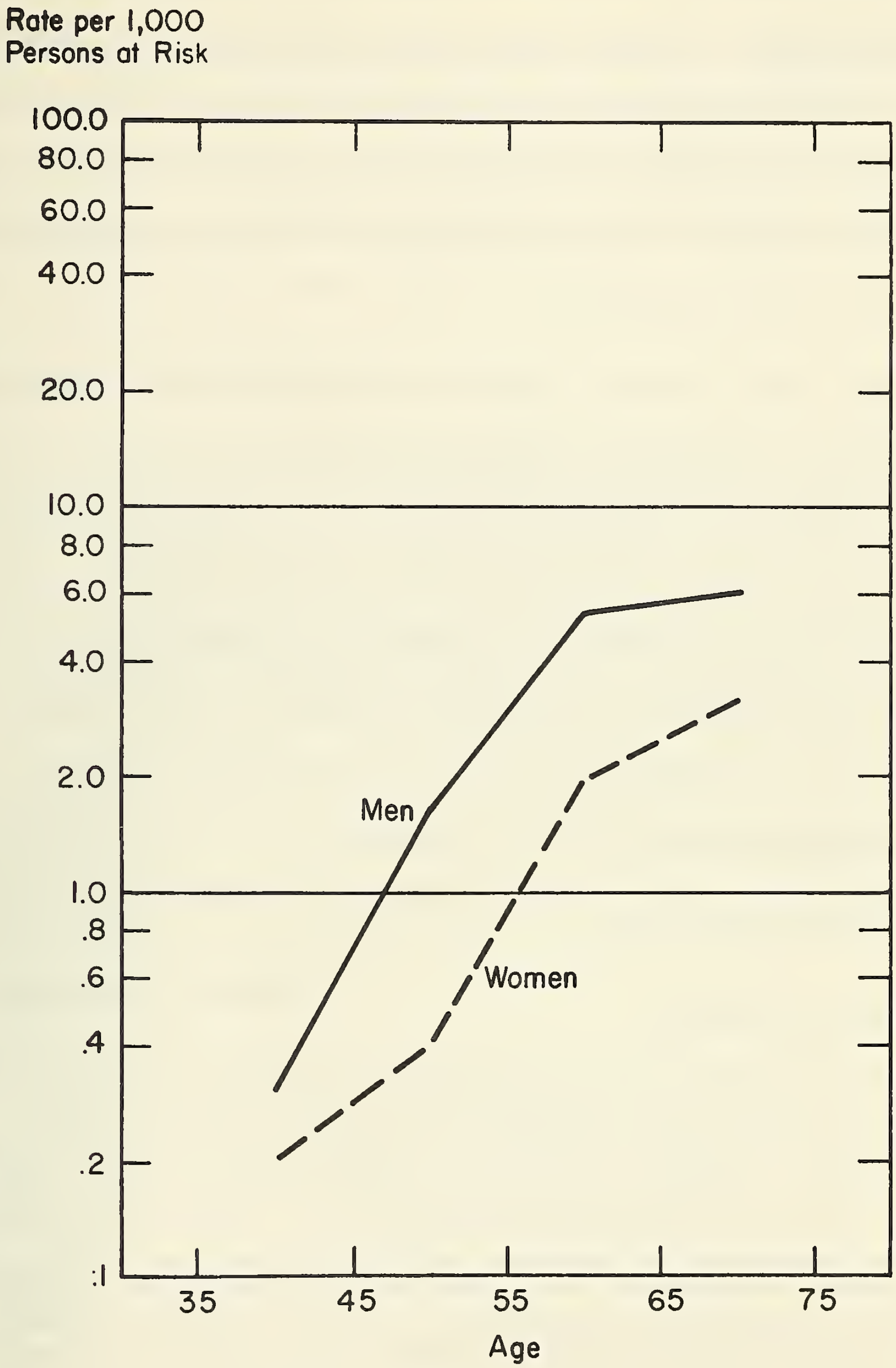


FIGURE 19

Average Annual Incidence Rate of Initial Events of Intermittent Claudication by Age and Sex, Framingham Study, 16-Year Follow-Up[6]



The various manifestations of CHD are:

Myocardial Infarction (See 4)

Coronary insufficiency. Coronary insufficiency was designated when a history of prolonged ischemic chest pain was accompanied by transient ischemic S-T segment and T-wave abnormality in the electrocardiographic tracing but not accompanied by development of Q-wave abnormality or by serum enzyme changes characteristic of muscle necrosis.

Angina pectoris. Brief recurrent chest discomfort of up to 15 minutes duration, precipitated by exertion or emotion and relieved by rest or by nitroglycerin, was regarded as angina pectoris (AP) if two physicians interviewing the subject agreed that this condition was definitely present. This diagnosis was based on evaluation of a subjective manifestation; no abnormality in the electrocardiographic tracing after exercise or at rest was required.

Sudden Death from CHD (See 5)

Nonsudden Death from CHD (See 7)

2. Cerebrovascular Accident

The diagnosis of overt vascular disease of the brain was based on the occurrence of stroke. Minimal criteria for *nonhemorrhagic* stroke consisted of the sudden onset of a localizing neurologic deficit (such as hemiparesis, aphasia, homonymous hemianopia); for stroke due to *intracranial* hemorrhage, a change in the state of consciousness, headache, and signs of meningeal irritation in association with a bloody spinal fluid under increased pressure whether with or without other localizing neurological deficits. A diagnosis of *embolus* to the brain was made if a source for embolus (that is, atrial fibrillation, rheumatic heart disease with mitral stenosis, recent myocardial infarction, bacterial endocarditis) was present, the clinical course consistent (that is, rapid onset and clearing, slightly bloody spinal fluid, a more localized deficit), or the occurrence of associated peripheral emboli elsewhere noted. A consultant neurologist and the clinical staff of the study reviewed hospital and clinic protocols.

3. Intermittent Claudication

Minimal criteria for the entirely subjective diagnosis of intermittent claudication consisted of a cramping discomfort in the calf clearly provoked by walking but not present on taking the first few steps, with pain appearing sooner when walking quickly or uphill and being relieved within a few minutes by rest. Interviews for symptoms of claudication were conducted by the physician using structured forms for uniformity of the assessment. In addition, a panel of investigators reviewed all cases suspected of claudication and confirmed the diagnosis.

4. Myocardial Infarction

Recent or *acute* myocardial infarction (MI) was designated when there were serial changes in the electrocardiograms indicating the evolution of an infarction, including: S-T segment elevation in the electrocardiographic tracing (ECG) associated with later inversion of T-waves and the loss of initial QRS potentials (that is, development of "pathologic" Q-waves of 0.04 second duration or greater), followed by serial changes indicating reversion towards normal. An *old* or *remote* myocardial infarction was considered to be present when the ECG showed a stable pattern including a pathologic Q-wave of 0.04 second duration or greater, or loss of initial QRS potential (R-wave) in those leads in which this would not be expected to occur. Also, an old MI was indicated when changes from a previous tracing showed development of loss of R-wave potential or appearance of pathological Q-waves not otherwise explained. More weight was given to this finding if a T-wave abnormality was also associated.

A hospital report for a subject showing a rise in the serum glutamic oxalacetic transaminase to a level of at least 60 units along with a history of prolonged ischemic chest pain was accepted as evidence of myocardial infarction. Subsequently, in 1962, pathologic elevation of another enzyme was included: lactic dehydrogenase greater than 500 units.

An autopsy report showing an acute, new, or recent infarction of the myocardium was accepted as evidence of MI. Because it is not possible to date an old MI found on autopsy, such evidence was not included in the clinical diagnosis.

5. Sudden Death from Coronary Heart Disease

If a subject, apparently well, was observed to have died within a few minutes (operationally documented as under one hour) from onset of symptoms, and if the cause of death could not reasonably be attributed to some potentially lethal disease other than coronary heart disease, this was called sudden death and was attributed to coronary heart disease.

6. Sudden Unexpected Death from Coronary Heart Disease

If a subject experienced sudden death and had no previous history of CHD, this was called sudden and *unexpected* death from coronary heart disease.

7. Nonsudden Death from Coronary Heart Disease

If the terminal episode lasted longer than one hour, if the available information implied that the cause of death was probably CHD, and if no other cause could be ascribed, this was called nonsudden death from CHD. In making this diagnosis the review panel used clinical information other than that concerning the final illness.

References

1. World Health Organization: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Vol 1. Geneva, WHO, 1957

2. National Center for Health Statistics: Vital Statistics of the United States, 1967: Volume II--Mortality, Part A. US Department of Health Education, and Welfare, Public Health Service. Washington DC, US Government Printing Office, 1969

3. Moriyama IM, Krueger DF, Stamler J: Cardiovascular Diseases in the United States. Vital and Health Statistics Monograph, American Public Health Assn. Cambridge, Harvard University Press, 1971, p 496

4. World Health Organization: World Health Statistics Annual, 1967. Volume I, Vital Statistics and Causes of Death, 1970. Geneva, WHO, 1970

5. Gordon T, Kannel WB: Premature mortality from coronary heart disease: The Framingham Study. JAMA 215:1617-1625, 1971

6. Shurtleff D: Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 16-year follow-up. An Epidemiological Investigation of Cardiovascular Disease, Section 26. Edited by WB Kannel, T Gordon. Washington DC, US Government Printing Office, 1970

7. Gordon T, Garst CC: Coronary Heart Disease in Adults, United States, 1960-1962. US Department of Health, Education, and Welfare, Public Health Service, Division of Health Examination Statistics, 1965. Washington DC, US Government Printing Office (PHS Publication No. 1000-Series 11-No. 10), p 46

8. Gordon T, Devine B: Hypertension and Hypertensive Heart Disease in Adults, United States, 1960-1962. US Department of Health, Education, and Welfare, Public Health Service, Division of Health Examination Statistics, 1966. Washington DC, US Government Printing Office (PHS Publication No. 1000-Series 11-No. 13), p 62

9. National Center for Health Statistics, National Health Interview Survey. Unpublished estimates for the average of fiscal years 1966 and 1967. Personal communication.

10. Nelson AB: Prevalence of Chronic Conditions and Impairments Among Residents of Nursing and Personal Care Homes. US Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics. Washington DC, US Government Printing Office (PHS Publication No. 1000-Series 12-No. 8), 1967

APPENDIX D

ECONOMIC IMPACT OF ARTERIOSCLEROSIS

The economic costs to the nation due to illness, disability, and death from the cardiovascular diseases and cancer were estimated for the year 1962 and published in the report of the President's Commission on Heart Disease, Cancer, and Stroke.[1] That report was followed by one containing estimates of the economic costs in 1963 of each major disease classification.[2] The report of the Second National Conference on Cardiovascular Diseases in 1964 also contained estimates of the economic costs of cardiovascular diseases.[3] These reports use the term "economic costs" or "economic impact" of a given disease to represent the annual benefits that would accrue to the economy if that disease were eliminated or controlled. These costs are further defined in the following terms:

1. Annual direct costs due to illness. These are the expenditures for prevention, detection, treatment, rehabilitation, research, training, and capital investment in medical facilities. In terms of types of services or object of medical expenditure, direct costs include amounts spent for hospital and nursing home care, physicians' and other medical professional service drugs, medical supplies, research, training, and other non-personal services.[2]

2. Indirect costs due to morbidity. These costs are measured by the lost earnings associated with man-years lost to productivity due to illness and disability.

3. Indirect costs due to mortality. These costs are measured in terms of the discounted present value of lifetime earnings of persons who died.

The discussion that follows provides estimates of the economic impact in 1967 of the major arteriosclerotic and hypertensive diseases. The estimating procedure and explanatory text closely follow that of the reports mentioned above. Separate estimates are made for the four major diagnostic components of these diseases coded to the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD)[4] as follows:

ICD 420-422	Arteriosclerotic and degenerative heart disease.
ICD 330-334	Vascular lesions affecting the central nervous system.
ICD 450-456	Diseases of arteries.
ICD 440-447	Hypertensive heart disease and other hypertensive disease.

Estimates of economic costs given in this report cannot be precise because: 1) Mortality and morbidity statistics corresponding to a precise definition of arteriosclerotic and hypertensive diseases are not available. For example, costs had to be included for all deaths from stroke even though about 20 percent of these deaths are not due to arteriosclerosis: 2) due to the lack of data, not all types of costs were computed, as explained below; and 3) much of the data on economic costs are derived from imprecise estimates. It should also be pointed out that only costs due to the arteriosclerotic and hypertensive diseases as the primary cause of illness or death are included. Costs of these diseases as a contributory factor to other illnesses cannot be estimated. This also means that costs for one type of arteriosclerotic and hypertensive disease as a contributory cause to another type cannot be separately identified.

In 1967, illness and mortality from arteriosclerotic and hypertensive diseases cost the nation an estimated \$23.9 million (Table 1). Of this total, the

TABLE 1

Estimated Economic Costs to the Nation due to Morbidity and Mortality from Arteriosclerotic and Hypertensive Diseases, United States, 1967*

Diagnosis	Amount (in millions)			
	Total	Morbidity		Mortality Costs**
		Direct Costs	Indirect Costs	
Total (Arteriosclerotic or hypertensive)	$23,887	$4,291	$1,133	$18,463
Arteriosclerotic Heart Disease	15,545	2,072	370	13,103
Stroke ***	4,605	971	235	3,399
Diseases of Arteries	1,082	354	31	697
Hypertensive Diseases ****	2,655	894	497	1,264

* From Table 2, 3 and 4.

** Present value of lifetime earnings (discounted at 6%) of persons who died of arteriosclerotic and hypertensive diseases.

*** Includes 20% not due to arteriosclerosis

**** Does not include all arteriosclerotic disease in which hypertension was involved.

direct costs amounted to $4.3 billion, of which $2.3 billion was for hospital care (Table 2). The $2.3 billion represents an estimated $1,100 per arteriosclerotic and hypertensive disease patient discharged from short-term hospitals. Approximately 228 million man-years of work were lost by members of the labor force and housewives due to illness from these diseases, amounting to indirect costs of morbidity of $1.1 billion (Table 3). The indirect costs due to mortality, represented by the present value of the remaining lifetime earnings of the 942,240 persons who died from these diseases in 1967, were $18.5 billion (Table 4).

DIRECT COSTS

Direct costs of illness represent expenditures for hospital and nursing home care, physicians' and other medical professional services, drugs, medical supplies, research, training, medical facilities construction, and other non-personal services. Estimates for these costs for all illnesses are prepared by the Social Security Administration. They are shown in Table 5 by type of expenditure.[5] The total national health expenditure was $50.8 billion in 1967.* The portion of these expenditures estimated for the arteriosclerotic and hypertensive diseases in 1967 is computed for the following expenditures: 1) hospital care, 2) physicians' services, 3) drugs, 4) nursing home care, and 5) medical professional services other than by physicians and dentists. Due to the lack of data, estimates of other health expenditures for these diseases could not be prepared. The procedures for

---

* A more current estimate (Fiscal Year 1970) is $67.2 billion which is not shown in the tables because the corresponding costs of arteriosclerotic and hypertensive diseases could only be estimated for 1967.

TABLE 2

Estimated Direct Costs of Morbidity from Arteriosclerotic and Hypertensive Diseases by Type of Expenditure, United States, 1967*

Diagnosis	Amount (in millions)					
		Type of Expenditure**				
	Total	Hospital Care	Physicians' Services	Drugs	Nursing Home Care	Other Medical Profess-ional Services
Total	$4,291	$2,253	$843	$599	$462	$134
Arteriosclerotic Heart Disease	2,072	1,280	319	237	171	65
Stroke	971	577	103	57	204	30
Diseases of Arteries	354	216	51	28	48	11
Hypertensive Diseases	894	180	370	277	39	28

* From Tables 6, 8, 9, 11 and 12

** Excludes expenditures for dentists' services, eyeglasses and appliances, prepayment and administration, government and other health services, research and medical facilities construction.

TABLE 3

Estimated Man-Years Lost to Productivity and Indirect Costs Due to Morbidity from Arteriosclerotic and Hypertensive Diseases; United States, 1967*

Diagnosis	Man-Years Lost to Productivity** (in millions)	Indirect Costs Due to Morbidity** (in millions)
Total	227.5	$1,133
Arteriosclerotic Heart Disease	63.3	370
Stroke	56.2	235
Diseases of Arteries	7.7	31
Hypertensive Diseases	100.3	497

* From Table 13

** Includes losses by currently employed persons and housewives.

TABLE 4

Estimated Indirect Costs of Mortality* from the Arteriosclerotic and Hypertensive Diseases, by Broad Age Group; United States, 1967**

Diagnosis	Amount (in millions)		
	Total	Under Age 65	Age 65 and Over
Total	$18,464	$11,135	$7,329
Arteriosclerotic Heart Disease	13,103	8,284	4,819
Stroke	3,399	1,760	1,639
Diseases of Arteries	698	324	374
Hypertensive Diseases	1,264	767	497

* Present value of lifetime earnings (discounted at 6%) of persons who died of arteriosclerotic and hypertensive diseases.

** From Table 26

TABLE 5

Aggregate National Health Expenditure by Type of Expenditure, United States, 1967[5]

Type of Expenditure	Amount (in millions)
Total	$50,763
Health Services and Supplies	47,054
Hospital care	18,029
Physicians' services	10,287
Drugs and drug sundries	5,652
Nursing home care	1,858
Other professional services	1,158
Dentists' services	3,360
Eyeglasses and appliances	1,609
Prepayment and administration	1,760
Government public health	942
Other health services	2,399
Research and Medical Facilities Construction	3,709
Research	1,703
Construction	2,006

estimating these five types of expenditures are explained below.

Hospital care. *Care of arteriosclerotic and hypertensive patients in the nation's short-term hospitals cost an estimated $2.3 billion in 1967 representing 29.4 million days of care* (Table 6). Unpublished provisional data from the Hospital Discharge Survey were provided by the National Center for Health Statistics on the total number of days of in-patient hospital care in 1967 and the number due to the arteriosclerotic and hypertensive diseases.[6] The Hospital Discharge Survey is a continuing probability sample of all short-term hospitals in the nation excluding military and Veterans Administration hospitals and hospital units of institutions. Short-term means under 30 days average stay per discharge. Patients were tabulated according to the diagnosis listed first on the summary sheet of the patients' records. The percent distribution of the number of days of care was applied to the amount of hospital care expenditures for all illnesses (from Table 5), to yield the estimated amount of hospital care expenditures due to arteriosclerotic and hypertensive diseases (Table 6). This method assumes that the estimated expenditures for hospital care are distributed by diagnosis similar to the distribution of hospital days of care by first-listed diagnosis.

Table 7 shows the estimated cost per arteriosclerotic and hypertensive patient discharged from short-term hospitals. The number of discharges includes inpatients discharged more than one time during 1967, whereas the costs are for both inpatients and outpatients. It is assumed that this has only a small effect on the cost per discharge.

TABLE 6

Estimated Number of Days of Hospital Care and Expenditures Due to Arteriosclerotic and Hypertensive Diseases, Short-Stay Hospitals in the United States, 1967[6]

Diagnosis	Number of Days of Care (in thousands)	Percent of Total	Amount of Expenditures (in millions)
Total - All Diagnoses	235,057	100.0%	$18,029
Arteriosclerotic and Hypertensive Diseases	29,373	12.5	2,253
Arteriosclerotic heart disease	16,578	7.1	1,280
Stroke	7,639	3.2	577
Diseases of arteries	2,860	1.2	216
Hypertensive diseases	2,296	1.0	180
Other Diseases	205,684	87.5	15,776

TABLE 7

Estimated Cost per Inpatient Discharged from Short-Stay Hospitals for Arteriosclerotic or Hypertensive Disease, United States, 1967

Diagnosis	Number of Discharges* (in thousands)	Hospital Care Costs** (in millions)	Cost per Hospital Discharge***
Total	1,994	$2,253	$1,130
Arteriosclerotic Heart Disease	1,137	1,280	1,126
Stroke	453	577	1,274
Diseases of Arteries	169	216	1,278
Hypertension	235	180	766

* From unpublished provisional data from the Hospital Discharge Survey

** From Table 6.

*** Hospital care costs divided by number of discharges.

Physicians' Services. Physician care of arteriosclerotic and hypertensive disease patients cost an estimated \$843 million in 1967, representing 105 million visits to physicians in private practice by these patients. Visit estimates were reported by the National Disease and Therapeutic Index on the total number of patient visits to physicians in private practice in 1967 and the number due to arteriosclerotic and hypertensive diseases (Table 8).[7] The National Disease and Therapeutic Index is a service of Lea Associates, Inc. of Ambler, Pennsylvania. It is a continuing study of private medical practice in the United States in which data are obtained from a representative sample of physicians who report case history information on private patients seen over a period of time.

In Table 8, the percent distribution of the estimated number of patient visits to physicians was applied to the total amount of expenditures for physicians' services (from Table 5), to yield the estimated amount of expenditures due to the arteriosclerotic and hypertensive diseases in 1967. This assumes that the estimated expenditures for physicians' services are distributed by diagnosis similar to the distribution of patient visits to physicians by diagnosis.

Drugs. An estimated \$599 million was spent for drugs in 1967 for the treatment of arteriosclerotic and hypertensive disease patients (Table 9). Estimates of patient visits to physicians were reported by the National Disease and Therapeutic Index according to whether or not medication was prescribed. In Table 9,[7] the percent distribution by diagnosis of visits for which medication was prescribed was applied to the total amount of expenditures for drugs (from Table 5), to yield the estimated amount of

TABLE 8

Estimated Number of Patient Visits to Physicians, and Expenditures for Physicians' Services Due to Arteriosclerotic and Hypertensive Diseases, United States, 1967[5,7]

Diagnosis	Number of Visits to Physicians (in thousands)	Percent of Total	Expenditures for Physicians' Services (in millions)
Total - All Diseases	1,284,817	100.0%	$10,287
Arteriosclerotic and Hypertensive Diseases	105,190	8.2	843
Arteriosclerotic heart disease	40,116	3.1	319
Stroke	12,449	1.0	103
Diseases of arteries	6,107	0.5	51
Hypertensive diseases	46,518	3.6	370
Other Disease	1,179,627	91.8	9,444

TABLE 9

Estimated Number of Patient Visits to Physicians for Which Drugs Were Prescribed, and Expenditures for Drugs Due to Arteriosclerotic and Hypertensive Diseases, United States, 1967[5,7]

Diagnosis	Number of Visits to Physicians for Which Drugs Were Prescribed (in thousands)	Percent of Total	Expenditures for Drugs (in millions)
Total - All Diseases	885,964	100.0	$5,652
Arteriosclerotic and Hypertensive Diseases	93,638	10.6	599
Arteriosclerotic heart disease	36,884	4.1	237
Stroke	9,148	1.0	57
Diseases of arteries	4,268	0.5	28
Hypertensive diseases	43,338	4.9	277
Other Diseases	792,326	89.4	5,053

expenditures due to the arteriosclerotic and hypertensive diseases in 1967. This assumes that the estimated expenditures for drugs are distributed by diagnosis similar to the distribution by diagnosis of patient visits to physicians when medication was prescribed.

Nursing Home Care. Data from a 1964 survey of nursing and personal care homes gives an estimated percent distribution of selected chronic conditions observed among the residents (Table 10).[8] These chronic conditions correspond approximately to the four diagnostic categories comprising the arteriosclerotic and hypertensive diseases. By applying this percent distribution to the estimated total expenditures for nursing home care in 1967, an estimated $462 million was expended for nursing home care for residents with arteriosclerotic and hypertensive disease (Table 11).

Other Medical Professional Services. Due to the lack of data, the portion of expenditures for other medical and professional services that was due to arteriosclerotic and hypertensive diseases had to be estimated by applying the percent distribution of the combined expenditures for hospital care, physicians' services, and nursing home care and drugs to the total expenditures for nursing home care and other medical professional services (Table 12). The total estimated costs of the arteriosclerotic and hypertensive diseases was $134 million for this category.

INDIRECT COSTS OF MORBIDITY

Productivity loss because of illness and disability from arteriosclerotic and hypertensive diseases cost the nation $1.1 billion in 1967 (Table 13). These losses are measured in terms of man-years of work lost and the economic value of the associated lost earnings. The estimated losses are given

TABLE 10

Percent Distribution by Diagnosis of the Number of Chronic Conditions Reported Among Residents of Nursing and Personal Care Homes, United States, May - June, 1964[8]

Diagnosis	Number of Conditions	Percent of Total Conditions
Total Chronic Conditions	1,703,700	100.0
Arteriosclerotic and Hypertensive Diseases	423,200	24.9
Diseases of the heart	156,500	9.2
Stroke	188,100	11.0
General arteriosclerosis	43,500	2.6
Hypertension without mention of the heart	35,100	2.1
All other Chronic Conditions	1,280,500	75.1

TABLE 11

Estimated Expenditures for the Care of Residents with Arteriosclerotic and Hypertensive Diseases in Nursing Homes, United States, 1967

Diagnosis	Percent of Conditions Reported in Nursing Homes*	Expenditures (in millions)
Total - All Diseases	100.0%	$1,858**
Arteriosclerotic and Hypertensive Diseases	24.9	462
Arteriosclerotic heart disease	9.2	171
Stroke	11.0	204
Diseases of arteries	2.6	48
Hypertensive diseases	2.1	39
Other Diseases	75.1	1,396

* From Table 10.

** From Table 5.

TABLE 12

Estimated Expenditures for Other Personal Care Services* for Arteriosclerotic and Hypertensive Diseases; United States 1967 5-7

Diagnosis	Expenditures for Hospital Care, Physicians' Services, Drugs and Nursing Home Care		Expenditures for Other Professional Services
	Amount** (in millions)	Percent of Total	
Total - all diseases	$35,826	100.0%	$1,158***
Arteriosclerotic and Hypertensive Diseases	4,157	11.6	134
Arteriosclerotic heart disease	2,007	5.6	65
Stroke	941	2.6	30
Diseases of arteries	343	1.0	11
Hypertensive diseases	866	2.4	28
Other Diseases	31,669	88.4	1,024

* Includes expenditures for medical professional services other than by physicians and dentists.

** From Tables 6, 8, 9 and 11.

*** From Table 5

TABLE 13

Summary of the Estimated Man-Years Lost and Indirect Costs Due to Morbidity From Arteriosclerotic and Hypertensive Diseases, by Broad Age Groups, United States, 1967*

Age	Total of These Conditions	Arteriosclerotic Heart Disease	Stroke	Diseases of Arteries	Hypertensive Diseases
	Man-Years Lost (in thousands)				
17 and over	227.5	63.3	56.2	7.7	100.3
17-44	22.2	6.4	1.7	-	14.1
45-64	105.5	36.6	16.1	1.9	50.9
65 and over	99.6	20.1	38.3	5.8	35.4
	Indirect Costs (in millions)				
17 and over	$1,133	$370	$235	$31	$497
17-44	116	40	7	--	69
45-64	632	249	79	12	292
65 and over	385	81	149	19	136

*From Tables 14 and 20

below for two population groups: 1) persons currently employed in the labor force, and 2) housewives. Due to the lack of data, losses are not estimated for: 1) persons in the labor force who are unable (or do not choose) to work at all, and 2) persons who reside in institutions (mental, tuberculosis, etc.) who otherwise would be in the labor force.

Currently Employed Population. Morbidity from the arteriosclerotic and hypertensive diseases among currently employed persons resulted in 80 million man-years of work lost, or $680 million in 1967 (Table 14). For the 12 months ending June 30, 1967, the estimated number of days lost from work associated with arteriosclerotic and hypertensive conditions was furnished by the National Center for Health Statistics from the National Health Interview Survey.[9] This is a continuing survey interviewing a representative sample of the nation's civilian, noninstitutionalized population, to determine the presence of acute and chronic conditions and the number of days of disability from these conditions. The average annual number of work-loss days was estimated for the period 1965 to 1967. Those coded to the arteriosclerotic and hypertensive diseases are given in this report. Estimates of work-loss days contain some duplication because disability might be due to more than one condition. It should also be pointed out that the variance of some of the estimates is very large.

In Tables 15 to 18 the estimated work-loss days were divided by 245, the approximate number of working days in a year, to obtain the number of man-years lost. Mean annual earnings, by age and sex, were then applied to the man-years lost to obtain the indirect costs for the currently employed population prevented from working due to arteriosclerotic and hypertensive diseases. The average annual earnings (wages and salaries before deductions)

TABLE 14

Summary of the Estimated Indirect Costs of Morbidity from Arteriosclerotic and Hypertensive Diseases Among the Currently Employed Population, United States, 1967 *

Age and Sex	Total of These Conditions	Arteriosclerotic Heart Disease	Stroke	Diseases of Arteries	Hypertensive Diseases
	Man-Years Lost (in thousands)				
Total	89.3	36.3	12.4	1.1	39.5
17-44	11.4	4.9	0.4	-	6.1
45-64	61.9	27.1	5.8	1.1	27.9
65 & over	15.8	4.1	6.1	-	5.6
Men	69.0	28.6	10.6	1.1	28.7
17-44	9.2	4.1	0.3	-	4.8
45-64	44.6	20.4	4.1	1.1	19.0
65 & over	15.1	4.0	6.1	-	5.0
Women	20.3	7.6	1.9	-	10.8
17-44	2.2	0.8	0.1	-	1.3
45-64	17.3	6.7	1.7	-	8.9
65 & over	0.7	0.1	-	-	0.6
	Indirect Costs (in thousands)				
Total	$679,671	$281,246	$91,425	$9,842	$297,158
17-44	80,457	35,021	2,754	----	42,682
45-64	489,395	217,513	45,562	9,842	216,478
65 & over	109,819	28,712	43,109	----	37,998
Men	576,018	242,103	82,083	9,842	241,990
17-44	70,269	31,316	2,291	----	36,662
45-64	399,037	182,519	36,683	9,842	169,993
65 & over	106,712	28,268	43,109	----	35,335
Women	103,653	39,143	9,342	----	55,168
17-44	10,188	3,705	463	----	6,020
45-64	90,358	34,994	8,879	----	46,485
65 & over	3,107	444	---	----	2,663

* From Tables, 15, 16, 17 and 18.

TABLE 15

Estimated Man-Years Lost to Productivity and Lost Earnings Due to Illness from Arteriosclerotic Heart Diseases, Currently Employed Persons, United States, 1967[9-12]

Age and Sex	Work-Loss Days (in thousands)	Man-Years Lost (in thousands)	Annual Mean Earnings	Lost Earnings (in thousands)
Total	8,883	36.3	-	$281,246
Men 17 & over	7,010	28.6	-	242,103
17-44	1,011	4.1	$7,638	31,316
45-64	5,010	20.4	8,947	182,519
65 & over	989	4.0	7,067	28,268
Women 17 & over	1,873	7.6	-	39,143
17-44	208*	0.8	4,631	3,705*
45-64	1,633	6.7	5,223	34,994
65 & over	32*	0.1	4,438	444*

* Figure does not meet standards of reliability or precision.[9]

TABLE 16

Estimated Man-Years Lost to Productivity and Lost Earnings Due to Illness from Stroke Currently Employed Persons, United States, 1967[9-12]

Age and Sex	Work-Loss Days (in thousands)	Man-Years Lost (in thousands)	Annual Mean Earnings	Lost Earnings (in thousands)
Total	3,048	12.4	-	$91,425
Men 17 & over	2,591	10.6	-	82,083
17-44	77*	0.3*	$7,638	2,291*
45-64	1,010	4.1	8,947	36,683
65 & over	1,504	6.1	7,067	43,109
Women 17 & over	457*	1.9*	-	9,342*
17-44	30*	0.1	4,631	463*
45-64	427*	1.7*	5,223	8,879*
65 & over	0	-	4,438	-

* Figure does not meet standards of reliability or precision.[9]

TABLE 17

Estimated Man-Years Lost to Productivitv and Lost Earnings Due to Illness from Diseases of Arteries, Currently Employed Persons, United States, 1967[9-12]

Age and Sex	Work-Loss Days (in thousands)	Man-Years Lost (in thousands	Annual Mean Earnings	Lost Earnings (in thousands)
Total	266*	1.1*	-	$9,842*
Men 17 & over	265*	1.1*	-	9,842*
17-44	0	-	$7,638	-
45-64	265*	1.1*	8,947	9,842*
65 & over	0	-	7,067	-
Woman 17 & over	0	-	-	-
17-44	0	-	4,631	-
45-64	0	-	5,223	-
65 & over	0	-	4,438	-

* Figure does not meet standards of reliability or precision.[9]

TABLE 18

Estimated Man-Years Lost to Productivity and Lost Earnings Due to Illness from Hypertensive Diseases, Currently Employed Persons, United States, 1967[9-12]

Age and Sex	Work-Loss Days (in thousands)	Man-Years Lost (in thousands)	Annual Mean Earnings	Lost Earnings (in thousands)
Total	9,685	39.5	-	$297,158
Men 17 & over	7,038	28.7	-	241,990
17-44	1,170	4.8	$7,638	36,662
45-64	4,655	19.0	8,947	169,993
65 & over	1,213	5.0	7,067	35,335
Women 17 & over	2,648	10.8	-	55,168
17-44	326*	1.3	4,631	6,020*
45-64	2,182	8.9	5,223	46,485
65 & over	139*	0.6*	4,438	2,663*

* Figure does not meet standards of reliability or precision.[9]

were estimated for full-time, year-round, civilian workers (Tables 19A and 19B). These estimates of earnings were obtained by increasing the estimates available for 1964[10] by the ratio of the median income of men and women in 1967[11] to the corresponding median income in 1964.[12] Average earnings for persons 14 to 44 years of age are assumed to be approximately the same as for individuals age 17 to 44.

Housewives' Services. Morbidity from arteriosclerotic and hypertensive diseases among housewives resulted in 138 million man-years lost from housework or $453 million in 1967 (Table 20). "Housewives' services are estimated at the average earnings of a domestic worker. This imputed value is clearly on the low side for it makes no allowance for the housewife's longer work week and takes no account of the size of the household cared for. Although the economic contributions of housewives are not included in the national income accounts, omitting the value of their services in the calculation of indirect costs distorts comparisons of costs among illnesses with different distributions by sex."[1]

Unpublished data from the National Health Interview Survey[9] provided the estimated number of days of disability in bed and days lost from work due to each of the arteriosclerotic and hypertensive diseases, by age, for women (Tables 21 to 24). The number of work-loss days was deducted from the bed disability days, and the resulting figure (adjusted bed disability days) was divided by 365 to obtain the estimated number of bed disability years attributed to these diseases. Multiplying this figure by the percent of women not in the labor force who keep house[13] (from Table 25) yields an

TABLE 19A

Computation of the Estimated Mean Annual Earnings of Men and Women Working Full-time Year-round, by Age, United States, 1967[10-12]

ge nd ex	Adjusted Mean Earnings 1964	Median Income 1964	Median Income 1967	Ratio of 1967 to 1964 Median Income	Mean Earnings 1967	Number of Persons with Income (in 1,000s)	Number of Persons times Mean Earnings 1967 (in millions)
en							
-19	$2,829	$ 2,364	$ 2,716	1.15	$ 3,253	3,186	$ 10,364
-24	4,634	4,339	5,312	1.22	5,653	4,809	27,185
-34	6,963	6,279	7,275	1.16	8,077	9,989	80,681
-44	8,131	6,969	8,078	1.16	9,432	10,676	100,696
-54	7,852	6,582	7,851	1.19	9,344	9,990	93,347
-64	7,148	6,027	7,024	1.17	8,363	6,775	56,659
+	5,939	4,599	5,488	1.19	7,067	2,058	14,544
men							
-19	3,387	2,830	2,927	1.03	3,489	2,496	8,709
-24	3,800	3,559	3,970	1.12	4,256	3,690	15,705
-34	4,307	3,893	4,491	1.15	4,953	4,587	22,719
-44	4,495	3,846	4,374	1.14	5,124	5,608	28,735
-54	4,507	3,775	4,445	1.18	5,318	5,799	30,839
-64	4,341	3,658	4,262	1.17	5,079	3,762	19,107
+	3,827	2,960	3,441	1.16	4,439	953	4,230

TABLE 19B

Computation of the Estimated Mean Annual Earnings of Men and Women Working Full-time Year-round, by Broad Age Groups, United States, 1967

Age and Sex	Number of Persons with Income (in 1,000's)*	Number of Persons Times Mean Earnings 1967 * (in millions)	Mean Earnings 1967
Men			
14-44	28,660	218,926	$ 7,638
45-64	16,765	150,006	8,947
65+	2,058	14,544	7,067
Women			
14-44	16,381	75,868	4,631
45-64	9,561	49,946	5,223
65+	953	4,230	4,438

*From Table 19A

TABLE 20

Summary of Estimated Man-Years Lost and Costs for Females Unable to Keep House due to Arteriosclerotic and Hypertensive Diseases, United States, 1967 *

Age	Total of These Conditions	Arteriosclerotic Heart Disease	Stroke	Diseases of Arteries	Hypertensive Diseases
	Man-Years Lost (in thousands)				
17 and over	138.2	27.0	43.8	6.6	60.8
17-44	10.8	1.5	1.3	--	8.0
45-64	43.6	9.5	10.3	0.8	23.0
65 and over	83.8	16.0	32.2	5.8	29.8
	Indirect Costs (In Thousands)				
17 and over	$453,435	$88,588	$143,707	$21,655	$199,485
17-44	35,435	4,922	4,265	---	26,248
45-64	143,052	31,170	33,794	2,625	75,463
65 and over	274,948	52,496	105,648	19,030	97,774

* From Tables 21-24

TABLE 21

Data for Estimating the Imputed Value of Earnings Lost Due to Arteriosclerotic Heart Disease, by Women Not in the Labor Force Who Keep House, by Broad Age Groups, United States, 1967 [9,13,14]

(Number in Thousands)

Age	Bed Disability Days	Work-Loss Days	Adjusted Bed Disability Days	Bed Disability Years	Percent Keeping House	Man-Years Lost by Women Who Keep House	Imputed Value of Lost Earnings
17 & Over	12,777	1,873	10,904	29.8	--	27.0	$88,588
17-44	876*	208*	668*	1.8*	83.7%	1.5*	4,922*
45-64	5,248	1,633	3,615	9.9	95.8%	9.5	31,170
65 & Over	6,653	32*	6,621*	18.1*	88.3%	16.0*	52,496*

* Figure does not meet standards of reliability or precision. [9]

TABLE 22

Data for Estimating the Imputed Value of Earnings Lost Due to Stroke, by Women not in the Labor Force Who Keep House, by Broad Age Groups, United States, 1967 [9,13,14]

(Number in Thousands)

Age	Bed Disability Days	Work-Loss Days	Adjusted Bed Disability Days	Bed Disability Years	Percent Keeping House	Man-Years Lost by Women who Keep House	Imputed Value of Lost Earnings
17 & over	18,271	457*	17,814*	48.8*	--	43.8*	$143,707*
17-44	573*	30*	543*	1.5*	83.7%	1.3*	4,265*
45-64	4,362	427*	3,935*	10.8*	95.8%	10.3*	33,794*
65 & over	13,336	0	13,336	36.5	88.3%	32.2	105,648

* Figure does not meet standards of reliability or precision. [9].

TABLE 23

Data for Estimating the Imputed Value of Earnings Lost Due to Diseases of Arteries, by Women Not in the Labor Force Who Keep House, by Broad Age Groups, United States, 1967 [9,13,14]

(Number in Thousands)

Age	Bed Disability Days	Work-Loss Days	Adjusted Bed Disability Days	Bed Disability Years	Percent Keeping House	Man-Years Lost by Women who Keep House	Imputed Value of Lost Earnings
17 & over	2,688	0	2,688	7.4	--	6.6	$21,655
17-44	0	0	--	--	83.7%	--	--
45-64	282*	0	282*	0.8*	95.8%	0.8*	2,625*
65 & over	2,407	0	2,407	6.6	88.3%	5.8	19,030

* Figure does not meet standards of reliability or precision.[9]

TABLE 24

Data for Estimating the Imputed Value of Earnings Lost Due to Hypertensive Disease, by Women Not in the Labor Force Who Keep House, by Broad Age Groups, United States, 1967 [9,13,14]

(Numbers in Thousands)

Age	Bed Disability Days	Work-Loss Days	Adjusted Bed Days	Bed Disability Years	Percent Keeping House	Man-Years Lost by Women Who Keep House	Imputed Value of Lost Earnings
17 & over	27,190	2,648	24,542	67.2	--	60.8	$199,485
17-44	3,814	326*	3,488*	9.6*	83.7%	8.0*	26,248
45-64	10,934	2,182	8,752	24.0	95.8%	23.0	75,463
65 & Over	12,442	139*	12,303*	33.7*	88.3%	29.8*	97,774*

* Figure does not meet standards of reliability or precision. [9]

TABLE 25

Computation of the Estimated Number of Females in the Noninstitutionalized Population, Not in the Labor Force, Who Keep House, by Broad Age Groups, United States, 1967 [13]

(Number in Thousands)

Age	Number of Females Not In Labor Force	Number Keeping House	Percent Keeping House
17-44	19,362	16,201	83.7%
45-64	10,806	10,353	95.8%
65 & Over	9,243	8,166	88.3%

estimate of the bed disability years for women who keep house, which is termed "man-years lost by women who keep house." The imputed economic value of these man-years lost is obtained by multiplying the man-years lost by the average wages of a domestic worker, which is $3,281 per year after adjustments for wage supplements.[14]

INDIRECT COSTS OF MORTALITY

The estimated indirect economic costs to the nation of the more than 942,000 deaths in 1967 from the arteriosclerotic and hypertensive diseases amounted to $18.5 billion (Table 26). Based on this estimate the indirect costs of mortality are represented by the product of the number of deaths from these diseases and the expected value of an individual's future earnings, with sex and age taken into account. The numbers of deaths by age, sex, and cause are published by the National Center for Health Statistics.[15] Unpublished discounted lifetime earnings by sex for five-year age groups are available for 1964 (Table 27).[10] These figures were increased by the ratio of the median income of men and women in 1967[11] to the median income in 1964.[12] This assumes that employment levels remain the same over these years. The present value of lifetime earnings (Table 27) was multiplied by the number of deaths from arteriosclerotic and hypertensive diseases, by age and sex, to yield the indirect costs of mortality from these diseases (Tables 28 to 31).

As stated elsewhere, the computation of lifetime earnings, as done for 1964, "required consideration of life expectancy for different age and sex groups, changing pattern of earnings at successive ages, varying labor force participation rates, imputed value for housewives' services, and the appropriate

TABLE 26

Number of Deaths from Arteriosclerotic and Hypertensive Diseases and the Estimated Indirect Costs due to These Diseases, United States, 1967

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	942,240	518,226	424,014	$18,464,258	$11,472,151	$6,992,107
Under 1	167	93	74	4,876	3,269	1,607
1-4	124	77	47	4,253	3,091	1,162
5-9	137	69	68	5,973	3,719	2,254
10-14	229	126	103	13,685	9,107	4,578
15-19	402	198	204	29,783	18,502	11,281
20-24	595	289	306	50,618	32,156	18,462
25-29	1,057	582	475	97,747	69,069	28,678
30-34	2,330	1,407	923	219,000	164,162	54,838
35-39	5,967	4,052	1,915	552,011	442,268	109,743
40-44	13,244	9,671	3,573	1,133,550	939,296	194,254
45-49	24,315	17,953	6,362	1, 76,391	1,458,609	317,782
50-54	39,388	29,130	10,258	2,318,168	1,860,999	457,169
55-59	58,546	42,340	16,206	2,606,458	1,975,542	630,916
60-64	80,208	55,149	25,059	2,322,949	1,513,344	809,605
65-69	107,172	67,109	40,063	1,986,653	936,842	1,049,811
70-74	138,610	79,373	59,237	2,187,541	922,949	1,264,592
75-79	157,581	80,577	77,004	1,926,104	717,296	1,208,808
80-84	148,007	67,484	80,523	1,035,028	348,892	686,136
84 & Over	164,161	62,547	101,614	193,470	53,039	140,431

* From Tables 28, 29, 30, and 31

TABLE 27

Estimated Present Value of Lifetime Earnings by Age and Sex, United States, 1964 and 1967

Age	Men		Women	
	1964 [9]	1967	1964 [9]	1967
Under 1	$30,251	$35,152	$18,955	$21,722
1-4	34,550	40,147	21,753	24,723
5-9	46,393	53,909	28,941	33,166
10-14	62,206	72,283	38,789	44,452
15-19	80,416	93,443	48,255	55,300
20-24	95,755	111,267	52,648	60,335
25-29	102,132	118,677	52,682	60,374
30-34	100,409	116,675	51,845	59,414
35-39	93,931	109,148	50,006	57,307
40-44	83,584	97,125	47,441	54,367
45-49	69,919	81,246	43,586	49,950
50-54	54,979	63,886	38,889	44,567
55-59	40,154	46,659	33,971	38,931
60-64	23,615	27,441	28,192	32,308
65-69	12,014	13,960	22,866	26,204
70-74	10,007	11,628	18,628	21,348
75-79	7,661	8,902	13,698	15,698
80-84	4,449	5,170	7,435	8,521
85 & Over	730	848	1,206	1,382

TABLE 28

Number of Deaths from Arteriosclerotic Heart Disease and the Estimated Indirect Costs Due to These Deaths, United States, 1967[10, 11, 12, 15]

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	625,688	370,949	254,739	$13,102,937	$8,854,368	$4,248,569
Under 1	51	34	17	1,564	1,195	369
1-4	30	16	14	988	642	346
5-9	27	13	14	1,165	701	464
10-14	38	25	13	2,385	1,807	578
15-19	106	74	32	8,685	6,915	1,770
20-24	168	114	54	15,942	12,684	3,258
25-29	421	302	119	43,025	35,840	7,185
30-34	1,215	891	324	123,207	103,957	19,250
35-39	3,774	3,027	747	373,199	330,391	42,808
40-44	9,444	7,764	1,680	845,416	754,079	91,337
45-49	18,057	14,663	3,394	1,360,840	1,191,310	169,530
50-54	29,777	23,813	5,964	1,787,115	1,521,317	265,798
55-59	44,499	34,259	10,240	1,997,144	1,598,491	398,653
60-64	59,888	43,494	16,394	1,723,176	1,193,519	529,657
65-69	76,514	50,400	26,114	1,387,875	703,584	684,291
70-74	94,674	56,629	38,045	1,470,667	658,482	812,185
75-79	101,524	54,439	47,085	1,223,756	484,616	739,140
8--84	90,354	43,072	47,282	625,572	222,682	402,890
85 & Over	95,127	37,920	57,207	111,216	32,156	79,060

TABLE 29

Number of Deaths from Stroke and the Estimated Indirect Costs Due to These Deaths, United States, 1967 [10,11,12,15]

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	202,131	93,046	109,085	$3,399,252	$1,607,594	$1,791,658
Under 1	107	53	54	3,036	1,863	1,173
1-4	86	57	29	3,005	2,288	717
5-9	101	50	51	4,386	2,695	1,691
10-14	151	85	66	9,078	6,144	2,934
15-19	199	95	104	14,628	8,877	5,751
20-24	262	121	141	21,970	13,463	8,507
25-29	426	186	240	36,564	22,074	14,490
30-34	684	311	373	58,447	36,286	22,161
35-39	1,334	615	719	108,330	67,126	41,204
40-44	2,332	1,120	1,212	174,673	108,780	65,893
45-49	3,892	1,922	1,970	254,557	156,155	98,402
50-54	5,939	3,128	2,811	325,113	199,835	125,278
55-59	8,627	4,810	3,817	373,030	224,430	148,600
60-64	12,621	7,019	5,602	373,597	192,608	180,989
65-69	19,515	10,404	9,111	383,985	145,240	238,745
70-74	28,668	14,643	14,025	469,675	170,269	299,406
75-79	37,187	17,264	19,923	466,435	153,684	213,751
80-84	37,824	16,046	21,778	268,528	82,958	185,570
85 & Over	42,176	15,117	27,059	50,215	12,819	37,396

TABLE 30

Number of Deaths from Disease of the Arteries and the Estimated Indirect Costs Due to These Deaths, United States, 1967 [10,11,12,15]

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	53,312	27,113	26,199	$697,608	$380,935	$316,673
Under 1	7	5	2	219	176	43
1-4	8	4	4	260	161	99
5-9	8	6	2	389	323	66
10-14	36	15	21	2,017	1,084	933
15-19	82	22	60	5,374	2,056	3,318
20-24	119	32	87	8,810	3,561	5,249
25-29	100	30	70	7,786	3,560	4,226
30-34	152	69	83	12,982	8,051	4,931
35-39	234	87	147	17,920	9,496	8,424
40-44	316	176	140	24,705	17,094	7,611
45-49	574	354	220	39,750	28,761	10,989
50-54	909	625	284	52,586	39,929	12,657
55-59	1,626	1,158	468	72,251	54,031	18,220
60-64	2,740	1,940	800	79,082	53,236	25,846
65-69	4,328	2,932	1,396	77,512	40,931	36,581
70-74	6,507	4,061	2,446	99,438	47,221	52,217
75-79	8,709	4,640	4,069	105,180	41,305	63,875
80-84	10,303	4,782	5,521	71,767	24,723	47,044
85 & Over	16,554	6,175	10,379	19,580	5,236	14,344

TABLE 31

Number of Deaths from Hypertension and the Estimated Indirect Costs Due to These Deaths, United States, 1967 [10,11,12,15]

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	61,109	27,118	33,991	$ 1,264,461	$629,254	$635,207
Under 1	2	1	1	57	35	22
1-4	--	--	--	--	--	--
5-9	1	--	1	33	--	33
10-14	4	1	3	205	72	133
15-19	15	7	8	1,096	654	442
20-24	46	22	24	3,896	2,448	1,448
25-29	110	64	46	10,372	7,595	2,777
30-34	279	136	143	24,364	15,868	8,496
35-39	625	323	302	52,562	35,255	17,307
40-44	1,152	611	541	88,756	59,343	29,413
45-49	1,792	1,014	778	121,244	82,383	38,861
50-54	2,763	1,564	1,199	153,354	99,918	53,436
55-59	3,794	2,113	1,681	164,033	98,590	65,443
60-64	4,959	2,696	2,263	147,094	73,981	73,113
65-69	6,815	3,373	3,552	137,281	47,087	90,194
70-74	8,761	4,040	4,721	147,761	46,977	100,784
75-79	10,161	4,234	5,927	130,733	37,691	93,042
80-84	9,526	3,584	5,942	69,161	18,529	50,632
85 & Over	10,304	3,335	6,969	12,459	2,828	9,631

discount rate to convert a stream of costs into its present worth."[16] Several of these economic concepts are briefly described below:

1. Cross-Sectional Earnings. "The appropriate measure for estimating the lifetime value of an individual's output is the mean earnings (wages and salaries before deductions) of men and women full-time, year-round civilian workers. The mean earnings in five-year age intervals are adjusted upward to take cognizance of wage supplements -- employer contributions for social insurance, private pension, and welfare funds. In the application of these cross-section survey data to the estimates of lifetime earnings, the assumption is that the future pattern of earnings for an average individual will remain the same as that reported for the base year. This model recognizes that the average individual may expect his own earnings to rise as he ages and gains experience in accordance with the cross-section data for the base year."[16]

2. The Discount Factor. "The value of money changes with time so that in order to calculate the present monetary value of man, his future expected earnings must be converted to their worth today. Banks and Kotz state that 'a given sum is normally worth more today than an equal sum at some future date, because the money (or resources) can be profitably invested (or consumed) in the interval between today and the future. Interest is the premium paid to reflect the fact that any given sum or resources could be put to profitable uses over a period of time...It follows that the value of money which is not currently available, but which will become available (or spent) some years hence must be discounted for the interest which could be earned in the interim, which is why the present value of a dollar

to be received in the future is always less than 100 cents.' The selection of the discount rate is most important since its effect is considerable. The higher the discount rate, the lower the present value of future earnings. ...The Bureau of the Budget recently issued a directive that the appropriate discount rate to be used by the government agencies in evaluating deferred costs and benefits is 10 percent. While future earnings must be discounted to reflect lost interest, average annual earnings must be increased to reflect gains in productivity. The discount rate, rather than the earnings, can be adjusted for expected changes in productivity...An assumption of 3.0 percent annual increase in productivity yields a net discount rate of 6 percent (1.10/1.03-1.06)."[16]

3. Allowance for Consumption. "In measurement of losses to an individual family, as calculated by insurance companies, consumption is treated as a deduction from a person's contribution to output. However, in measurement of losses to society, as calculated here, consumption is viewed as an end in itself and therefore not deducted from lost earnings."[16] This treatment of consumption is explained more fully by Klarman in the following quote: "Diversity of opinion still prevails regarding the treatment of consumption. Insurance companies and families should, of course, deduct consumption in their calculations of the economic value of a man. Unlike insurance companies or families, society as a whole is concerned with total output, of which consumption is the major component. Man is not a machine, and consumption is the ultimate goal of economic activity. On this basis, net production after consumption is not relevant to the economist's central concern, and consumption should not be deducted."[3] Fein also interprets consumption as an end in itself in the following quote: "Certainly the net

figure (gross value less consumption) derived by Dublin and Lotka to indicate the money value of a man to his family is correct for their purposes. It is not at all apparent, however, that the net concept is the correct one when we deal with the economic value of a man to society. It is true that man consumes partly in order to maintain himself, and in this sense some of his consumption may be considered as a gross investment to take care of his depreciation; it is also true, however, that consumption is an end in itself and can be viewed as a final, rather than an intermediate, step in the creation of other products.[17]

References

1. The President's Commission on Heart Disease, Cancer, and Stroke: A National Program to Conquer Heart Disease, Cancer and Stroke. Volume 2, February 1965

2. Rice DP: Estimating the Cost of Illness; Health Economics Series No 6, USPHS Publication No 947-6, May 1966

3. Klarman HE: Socioeconomic Impact of Heart Disease, Second National Conference on Cardiovascular Diseases, Washington DC, 1964, Volume II, 1965

4. World Health Organization: Manual of the International Classification of Diseases, Injuries, and Causes of Death, Volume I, 1957

5. Social Security Administration, Research and Statistics Note No 25, National Health Expenditures, Fiscal Years 1929-70 and Calendar Years 1929-69, December 14, 1970

6. National Center for Health Statistics, Division of Health Resources Statistics, Hospital Discharge Survey Branch; unpublished provisional information obtained by personal communications

7. Lea Incorporated, National Disease and Therapeutic Index, Reference File for June 1966 to July 1967

8. Nelson AB: Prevalence of Chronic Conditions and Impairments Among Residents of Nursing and Personal Care Homes, PHS Publication No 1000, Series 1000, No 8, July 1967, National Center for Health Statistics

9. National Center for Health Statistics, Division of Health Interview Statistics. Unpublished information obtained by personal communication

10. Department of Health, Education, and Welfare, Office of the Assistant Secretary for Program Coordination: Motor Vehicle Injury Prevention Program, August 1966. Program Analysis. Disease Control Programs 1966-1. Washington, DC

11. Department of Commerce, Bureau of the Census: Current Population Reports, Consumer Income, Series P-60, No 60, 1969

12. Department of Commerce, Bureau of the Census: Current Population Reports, Consumer Income, Series P-60, No 47, 1965

13. Department of Labor, Bureau of Labor Statistics: Employment and Earnings and Monthly Report on the Labor Force, Vol 14, No 7, 1968

14. Department of Commerce: Survey of Current Business, 1968

15. National Center for Health Statistics, Division of Vital Statistics: Vital Statistics of the United States, 1967, Vol II, Part A, 1969

16. Rice DP, Cooper BS: Cost of Accidents (unpublished)

17. Fein R: Economics of Mental Illness. New York, Basic Books, 1958, pp 18-19

APPENDIX E

IMPACT OF BASIC RESEARCH ON THE PRACTICE OF MEDICINE: EXAMPLES FROM THE FIELD OF ARTERIOSCLEROSIS

Basic Research

Scientists, including medical investigators, have been criticized for their failure to explain adequately to the public and public officials the need for continued investment in people and facilities; investments that will optimize research in a variety of scientific fields. There are probably many reasons for this failure. Many of the most productive scientists spend long hours in their laboratories or clinics, pursuing clues and solving scientific puzzles. They are thoroughly convinced about the importance of their work for the society in which they live, but they usually give little thought to sharing their excitements and convictions with others outside their special field. In many instances barriers of a technical nature make it all but impossible to publicize the most recently acquired knowledge without gross distortions of the essential elements.

Although science writers are informing the public about new developments in science, they tend to concentrate their efforts on innovations with readily identifiable practical consequences. Medical discoveries are frequently presented as the result of one or more year's work by investigators who tried to solve a specific medical problem. Rarely is the public given the opportunity to learn about the complicated interactions between earlier developments in apparently unrelated fields which laid the groundwork for the later work. This account was written to show that certain developments in the physical and biological sciences more than 50 years ago are coming to fruition in providing a better understanding of the mechanisms of atherogenesis and thereby leading to improved diagnosis and treatment of the disease.

Arteriosclerosis

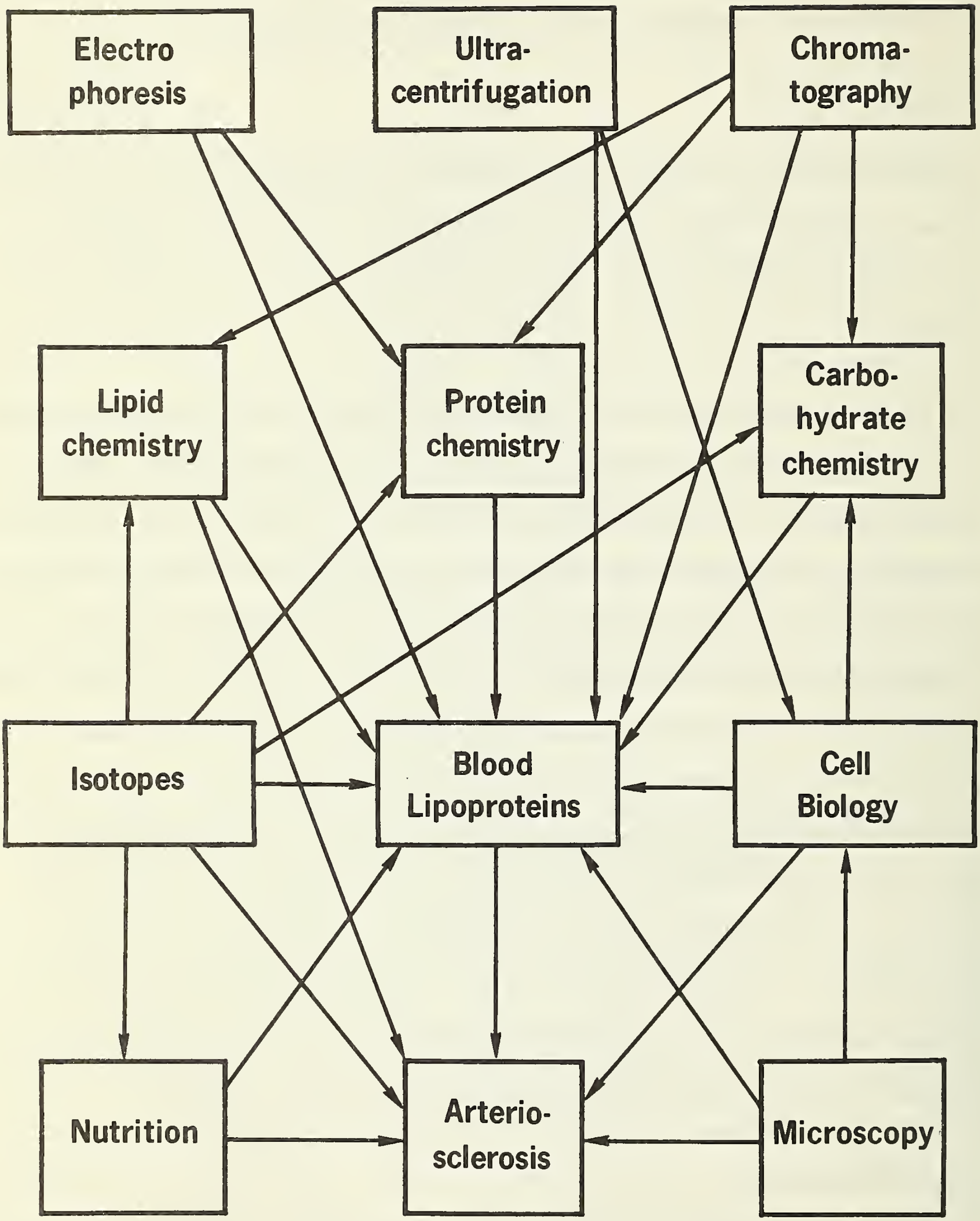
Arteriosclerosis is readily recognized when it has reached a very dangerous stage, as when a person becomes the victim of a heart attack or stroke. At this stage the disease is near its endpoint: death or prolonged disability.

Considerable progress has been made in identifying elements of this disease pattern long before the condition reaches the irreversible stage. Some of these elements are: cholesterol deposition in the arterial wall, fibrosis, hemorrhage, thrombosis, and calcification. Some of the scientific developments that have produced major advances in our understanding of this complex disease are shown in Figure 1. At the top are three technical and methodological developments for the quantitative analysis of lipids, proteins, and carbohydrates. The quantitative knowledge, combined with the use of radioactive isotopes and biochemical studies of cell components, has led to understanding of the structure and metabolism of blood lipoproteins. One or more of these lipoproteins are major factors in the development of arteriosclerosis. In the following sections we have traced the impact of some major developments in the basic sciences on our current knowledge about blood lipoproteins and arteriosclerosis.

Ultracentrifugation

When in 1908 T. Svedberg obtained his Ph.D. in physical chemistry at the

FIGURE 1


Electro phoresis
Ultra-centrifugation
Chroma-tography
Lipid chemistry
Protein chemistry
Carbo-hydrate chemistry
Isotopes
Blood Lipoproteins
Cell Biology
Nutrition
Arterio-sclerosis
Microscopy

University of Uppsala he could not know that his graduate work on the preparation of colloidal metal particles, which were too small to be seen with a microscope, was the first step on the road to a discovery of major medical importance. And even today scientists, working on the structure of lipoproteins in the bloodstream, are unaware that one of the principal tools used in their studies was developed to satisfy the curiosity of a colloid chemist.

Svedberg was aware, of course, that blood cells can be separated from the plasma by letting a tube of whole blood stand for an hour or so. The cells, being heavier than plasma, settle slowly under the influence of gravity. He also knew that the effects of gravity can be enhanced a thousandfold by spinning the blood in a laboratory centrifuge.If he could devise a centrifuge which outperformed the laboratory model by several hundred or a thousandfold, he was sure that he could sediment his metallic particles, and learn a great deal about their properties. However, many engineering problems faced him. The tubes and rotors, used in the laboratory centrifuge, exploded when they were subjected to the immense forces developed in an "ultracentrifuge." Frictional forces between the rotor and air overheated the rotor and heated the samples inside.

Partly as the result of research performed at the University of Wisconsin in the early twenties, Svedberg was able to solve these problems. In 1926 he was awarded the Nobel Prize in Chemistry and Physics for this work and the application to the study of proteins.

One more step was needed before the ultracentrifuge could be applied to the study of lipoproteins, which, by the way, were not even known to exist in 1926. It seems a simple step now, but no one had thought of it until 1949 when Dr. Gofman and colleagues, at the University of California, reported that lipid-protein complexes of blood plasma could be separated in the ultracentrifuge in much the same way that cream is separated from whole milk. They showed that by increasing the density of blood plasma with salt before ultracentrifugation, the lipoproteins floated to the surface. Shortly after this discovery, Gofman and his colleagues in Berkeley, as well as biochemists elsewhere, were able to exploit this method, not only for the study of lipoprotein chemistry, but also as a diagnostic tool for lipoprotein abnormalities which appeared to be related to the causes of arteriosclerosis. While these studies were going forward, A.W.K. Tiselius, contributed unwittingly to another major development in the diagnosis of lipoprotein abnormalities.

Electrophoresis

Tiselius studied chemistry at Uppsala and became an assistant to Svedberg at about the time that Svedberg received the Nobel Prize for his work on the ultracentrifuge. Tiselius was assigned the task of separating large molecules such as proteins. After about five years, in 1930, Tiselius presented his doctoral dissertation on the separation of proteins according to their electrical charge. In 1949 he was awarded the Nobel Prize for this and other work on protein separation. Although Tiselius' electrophoretic methods were used extensively for the quantitation of blood proteins, it took other developments before electrophoresis became a useful method in the separation and assay of serum lipoproteins. In the early sixties the work of Svedberg, Tiselius, and many other scientists finally provided clinical laboratories all over the world with tools for the diagnosis of lipoprotein abnormalities.

Chromatography

In 1906 a Russian botanist, M. Tswett, published the first chromatographic method for the separation of plant pigments. The method was so simple, and esthetically so pleasing, that it is difficult to understand why it took some 25 to 30 years before other scientists began to use similar methods in other fields. Tswett applied extracts of plant materials to a small piece of paper and showed that he could separate multicolored bands by letting a small amount of solvent displace the pigments.

Although the method was used by industrial chemists to separate dye-stuffs no one extended it beyond this limited application until shortly before World War II. At that time the International Wool Secretariat, representing the wool growers of Australia, New Zealand, and South Africa, became concerned about the increasing use of artificial fibers. Among other things, the Secretariat decided to support fundamental studies on the composition of wool fibers. They gave a fellowship to R.L.M. Synge of Cambridge, England, to devise analytical methods for the study of wool proteins. Synge, with the help of A.J.P. Martin, extended Twsett's method by developing and testing a theory of "partition chromatography." They utilized silica, starch resins, and paper for the quantitative analysis and preparation of proteins, carbohydrates, lipids, antibiotics, vitamins, and a host of other organic and inorganic materials. Their work was recognized by the award of the Nobel Prize in 1952. The methodology, started by Martin and Synge, and adapted by many others to their own specialties, had an unparalleled impact on the development of lipid and lipoprotein methods. In particular, thin layer chromatography and gas liquid chromatography made it possible to quantitate the lipid fractions of blood in about 1/100th to 1/1000th of the time required previously.

With the help of chromatography, electrophoresis, and ultracentrifugation medical scientists can uncover risk factors for arteriosclerotic heart disease even in infants at birth. Apparently one out of every hundred infants has an elevation of blood lipoproteins that increases his risk of heart disease in later life--a risk that we may be able to lower by appropriate alterations in diet for some, and by drug therapy for others. The Swedish, British, and Russian scientists were solving problems in areas far removed from medical practice, but people all over the world have benefited from their research by improved diagnosis and treatment of cardiovascular disease.

Radioactive Isotopes

The methods described so far gave great impetus to the development of modern medicine. But the application of radioactive isotopes to the study of physiology and biochemistry introduced an entirely new dimension to our understanding of biological processes. Before World War I, biologists thought of living organisms as static structures, machines which were subject to wear and tear. Organs and tissues were thought to be renewable to a limited extent, only when a part had been injured or worn out. George de Hevesy, an inorganic chemist turned physicist, had little opportunity to think about the life processes. As a post graduate student with

Rutherford in Manchester he was given the task of separating radium D from other radium isotopes, including lead. He failed in this intent. However, he turned his failure into success by using radium D as a tracer for lead in chemical reactions, much as tracer bullets are used to follow the path of bullets in the same stream.

De Hevesy was still far removed from biological applications. Tracing chemicals was of little value to the biologist until radioactive isotopes of biologically important elements became available. This happened more than 20 years later, in 1934, when de Hevesy produced a small quantity of radioactive phosphorus by bombarding carbon disulfide with neutrons. In collaboration with others, de Hevesy traced the path of phosphates in animal food through many biochemical reactions. These reactions are now known to be the basis for the intracellular release and storage of energy. But of more fundamental importance was the discovery that every organ in the body is "turning over" at a rapid rate. The molecule of phosphate present in a red blood cell might be in the spleen as part of its energy generating system a few minutes later, and in another minute or two find its way into the structural components of the skeleton.

Biologists and medical researchers were quick to recognize the new insight about the chemistry of living beings. The major limitation at first was the lack of radioisotopes of biological interest, and the extremely minute quantities of those that were available.

The development of the cyclotron improved the situation considerably, but radioactive isotopes were available primarily in places where physicists were busily splitting atoms. The real push in the production of radioactive isotopes came with the Second World War and the development of atomic weapons. Although isotopes for medical studies were still a side product of the gigantic arms race, the prospects of radiation damage from bombs and nuclear furnaces made it imperative that effects of isotopes be investigated.

We seem to have strayed rather far from the subject of arteriosclerosis. But, in fact, have we? When, after World War II, long life radioactive carbon became available in large quantities, the door to metabolic studies was opened. Physicists, chemists, and biologists joined hands in the venture. Today, some 25 years later, medical scientists in many universities and hospitals are studying the control of cholesterol synthesis by organs within the human body. They now know that in addition to dietary cholesterol, the synthesis of cholesterol by liver and intestines is an important source of blood cholesterol. They are studying the mechanisms whereby this cholesterol, which is found in the blood lipoproteins, is deposited in the arterial wall and they are slowly identifying possible control points in this process. A joint Nobel Prize for the study of cholesterol biosynthesis with radioactive carbon was awarded in 1964 to Konrad Bloch at Harvard and to Feodor Lynen in Munich. The Nobel Prize for George de Hevesy, the physicist who started it all, was awarded in 1943.

Conclusions

The diagram in Figure 1 shows only a few of the many developments that have impinged upon our present day knowledge of arteriosclerosis, a knowledge that still is pitifully small. The blocks in Figure 1 are not independent. Tiselius, the discoverer of electrophoresis, was a student of Svedberg, the developer of the ultracentrifuge. The ultracentrifuge is used widely in the study of proteins and nucleic acids and in cell fractionation, fields of immense importance in the study of metabolism.

The blocks singled out for extensive discussion did not originate in medically oriented research programs, although similar developments have come about as a direct result of research by physicians, biochemists, and other paramedical scientists. But the purpose of this discussion is to support the often repeated formula that "basic research is good for society." We have, therefore, concentrated our attention on several physicists, chemists, and a botanist whose discoveries some 30 to 60 years ago have had, and are continuing to have, a major impact on the development of medical science and the delivery of medical care.

Bibliography

Most of the biographical material was taken from:

Nobel Prize Winners in Chemistry 1901-1950. E Farber, editor, H Schuman, New York, 1953

Nobel Prize Winners in Medicine and Physiology 1901-1965. TS Sourkes, editor. London, New York, Abelard-Schuman, 1966

U.S. G.P.O. 1972/481-991/3002/253

DATE DUE

NIH LIB NOV 12 19[illegible]

MAR 2 1977

[illegible]

NIH LIB SEP 8 1975

MAR [illegible] 1977

MAY 25 1977

NOV [illegible]

MAY [illegible]

PRINTED IN U.S.A.

NIH LIBRARY
Amazing Research.
Amazing Help.

http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
4 0080 9162

NIH LIBRARY
3 1496 00192 4003

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DHEW Publication No. (NIH) 72-219